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BACIU ANATOLIE

PROGRAM OF NEUROPROTECTION AND NEUROREHABILITATION BASED ON THE COMBINED MULTIMODAL ACTION OF ENVIRONMENTAL FACTORS, INDIVIDUAL DAILY ACTIVITY AND ECOLOGICAL NUTRITION

165.01 – HUMAN AND ANIMAL PHYSIOLOGY

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CONTENT

CONCEPTUAL LANDMARKS OF THE RESEARCH…….…….... 4
THESIS CONTENT……..……... 6
1. JUSTIFICATION OF THE URGENT NEED TO DEVELOP A NEUROPROTECTION AND NEUROREHABILITATION PROGRAM TO MAINTAIN HUMAN RESOURCES (SITUATION ANALYSIS IN THE FIELD OF THE THESIS).……..... 6
2. MATERIALS AND METHODS…….……... 9
2.1 Selection of groups of experimental laboratory animals and individuals appropriate to the occupation, design of experiments and occupational models..... 9
2.2 Neurosurgical methodology for implantation of chronic polysomnography electrodes based on stereotactic technique in animals..... 10
2.3 Methods of assessment of psychomotor, somatosensory and somatomotor reflex activity in the daily activity mode..... 13
2.4. Methodology for assessing the neuromodulatory action of brain monoaminergic neurotransmitter systems using high-performance liquid chromatography (HPLC)..... 13
2.5. Assessment of protein biosynthesis in neurons and neuroglial satellites based on histochemical analysis of the amount of nucleic acids in cellular compartments..... 14
2.6. Assessment of monoamine breakdown by enzymatic activities of monoamine oxidase A and monoamine oxidase B and protein cleavage by proteolytic activity of cathepsin D..... 14
2.7. Application of biochemical methods to study carbohydrate and lipid metabolism in aerobic and anaerobic training..... 14
2.8. Application of the statistical laws of variation to determine the validity of the difference between the groups studied..... 14
3. NEUROPROTECTION AND NEUROREHABILITATION PROGRAM, RESULTS OF ITS TESTING IN EXPERIMENTAL MODELS AND IN THE "PERSON-ENVIRONMENT-OCCUPATION-PERFORMANCE" MODEL..... 15
3.1. Testing Step 1 of the neuroprotection and neurorehabilitation program, based on sufficient functional gas exchange in the body..... 15
3.2. Testing Step 2 of the neuroprotection and neurorehabilitation program, which ensures that the limits of neuroplasticity are extended by optimizing daily activity and diet..... 20
3.3. Testing Step 3 of the neuroprotection and neurorehabilitation program, which aims to extend the limits of neuroplasticity by balancing circadian rhythms..... 21
3.4. Testing Step 4 of the neuroprotection and neurorehabilitation program, characterized by the inclusion of plant-derived adaptogens in the daily nutrition……..…… 24
3.5. Conceptual elaboration of Step 5 of the neuroprotection and neurorehabilitation program, based on the inclusion of organic agricultural products in the daily nutrition……..…… 27
3.6. Step 6 testing of the neuroprotection and neurorehabilitation program, including balance and sensorimotor integration..... 28
3.7. Conceptual development of Step 7 of the neuroprotection and neurorehabilitation program, based on the application of biomedical engineering achievements..... 32
3.8. Conceptual development and testing of Step 8 of the neuroprotection and neurorehabilitation program, which requires the introduction of bioinspiration and biofiltering environmental design technologies..... 34
GENERAL CONCLUSIONS AND RECOMMENDATIONS……..... 38
BIBLIOGRAPHY (selective)…….……..……..... 39
LIST OF THE AUTHOR'S PUBLICATIONS ON THE THESIS TOPIC……..……..... 41
ANNOTATION (in Romanian, English and Russian)…….……..……..... 48

CONCEPTUAL LANDMARKS OF THE RESEARCH

Actuality and importance of the topic addressed. The loss of qualified human resources or quantitative and qualitative human capital is particularly relevant for the Republic of Moldova, based on alarming statistics regarding demographic changes, depopulation of settlements, increased morbidity and mortality, signs of degradation of terrestrial, coastal maritime and aquatic ecosystems. For example, in 1989 it was already established that approximately 35 million US citizens have physical or mental disabilities that interfere with their daily activities. More than 9 million of these people are so severely affected that they cannot work, go to school, or run a business. Disability is considered the biggest problem of the human population, even in socio-economically overdeveloped countries. Many medically, socially and economically important issues draw attention to the need to develop an effective national disability prevention program. As the number of people surviving in life-threatening environmental conditions increases, quality of life issues need to be more widely taken into account in the decisions of government agencies. The need to intensify the search for effective strategies to prevent disability is also emphasized by a senectectute population. According to the World Bank report in Moldova, the share of the elderly by 2060 could increase significantly and reach up to 30%. For example, in the United States by 2020, there were 51.4 million people over 65, which represents 17.3% of the population, compared to 31.7 million and 12.7% respectively in 1990. Moldova spends 10 percent of GDP on the health sector. This share is comparable to developed countries, but the costs alone do not lead to a healthier population. In addition to the fact that the declining working capacity of the population has a strong impact on GDP, the treatment and care of patients with physical and mental disabilities is a major cost element in public policies. In the United States, these figures amount to 149.4 billion dollars.

Aim of the work (or overall objective): development of a fundamental scientific basis, experimental testing and application in health screening of occupationally active people under certain environmental conditions and of a technological approach based on sensory-motor exercises under optimized conditions for the prevention of neurodegenerative diseases (Alzheimer, Parkinson)

Research objectives:

- application of high-performance laboratory methods for the applied study and demonstration of the basic mechanisms of neuroprotective, neurorecovirative action of the multimodal combination of environmental factors, intensified activity and optimized nutrition;
- determination of the neuromodulatory and neuroprotective action of brain monoaminergic systems triggered by combined hypoxia/hypercapnia by application of High Performance Liquid Chromatography (*HPLC*) and electrochemical detection;
- examination of monoaminergic neuromodulation of neuroplasticity changes by measuring the amount of nucleic acids in subcellular compartments of satellite neurons and neuroglial cells in the coordination centers of sensory processing and environmental signal generation, characteristic of the modulating and coordinating action of central monoaminergic systems during sensorimotor integration of proprioceptive perception;
- testing the modulatory and coordinating effect of monoaminergic systems under conditions of desynchronization of internal circadian sleep-wake circadian biorhythmicity with environmental *zeitgebers*;
- to search for criteria for the evaluation of neurodegeneration processes by measuring the monoamine oxidase and proteolytic enzyme activity of cathepsin D in brain formations of physically and psycho-emotionally overstrained individuals during daily individual activity;
- detection of the manifestations of neurodegenerative processes as a result of total sleep deprivation and selective deprivation of rapid eye movement sleep (*REM sleep*) by assessing the

degradation of catecholaminergic neurotransmitter catecholaminergic neurotransmitters and the ratio of anabolic and catabolic protein activities;

- estimation of the prevalence of neuroplastic (neuroprotective) remodeling and/or neurodegenerative changes in the function of sensory-motor effort dosage during work activity (service) or aerobic and anaerobic training; to approve the action of the combination of physical environmental factors (hypoxia, hypothermia) with aerobic, anaerobic strength effort and optimized nutrition on the plasticity of the neuro-muscular apparatus and metabolic balance;
- elaboration of the Conceptual and Strategic Programme for the organization of ecological communities and centres for health Improvement through neuroprotection, neurorehabilitation and prevention of neurodegenerative diseases with the application of organic nutrition.

Research hypothesis: by strictly following a systematic programme of designing and organizing the workplace and habitual environment, planning daily activities and ensuring an optimized diet of organic food, it is possible to significantly support the neuroprotective properties of the brain's neural regulatory neural regulatory networks, neuroendocrine, endocrine and immunomodulatory mechanisms and maintain vitality**.**

Synthesis of research methodology and justification of chosen research methods: application of High Performance Liquid Chromatography (HPLC) and electrochemical detection for the analysis of monoamines and their metabolites in the tissue of nerve regulatory centers; measurements of nucleic acid content in subcellular compartments of neurons and satellite neuroglia cells in the centers coordinating sensory processing and motor command generation using histochemical analysis; estimation of the reactivity of biosynthesis of neurotropic factors by the application of immunohistochemical analysis; determination of monoamoxidase and proteolytic enzyme activity of cathepsin D in brain formations; electrophysiological, neurological, biochemical laboratory examinations and functional tests for estimation of sleep-wake circadian biological rhythm desynchronization and neuronal activity asymmetry in an experimental and occupational model; experimental modeling of the action of hypoxia and hypercapnia in laboratory animals; experimental modeling of sensory-motor training in these animals; experimental modeling of sleep-wake circadian cycle desynchronization by applying the "*Night shift work*" model (forced activity) and selective deprivation of Rapid Eye Movement (REM) sleep; conceptual and strategic development of the Neuroprotection and Neurorehabilitation Program based on the application of environmental factors and ecological nutrition.

Summary of thesis chapters:

Chapter 1. "JUSTIFICATION OF THE URGENT NEED TO DEVELOP A NEUROPROTECTION AND NEUROREHABILITATION PROGRAM TO MAINTAIN HUMAN RESOURCES (SITUATION ANALYSIS IN THE FIELD OF THE THESIS)"

The current status of the problem of formation, development, preservation and rehabilitation of sufficient functionality and adaptability of neuronal regulatory formations, sensory systems, neuromuscular apparatus in relation to the multimodal impact of environmental factors, peculiarities of daily activity, work and recreation, sleep and wakefulness, balance of energy and plastic metabolism is sufficiently demonstrated. Each of the 8 subchapters covers a specific, but at the same time complex problem, reflected in the algorithm of the developed neuroprotection and neurorehabilitation program. The main importance is given to the problem of adequate gas exchange in the body in its close interaction with the circulatory system, in particular the cerebral circulation, depending on the specific conditions of work activity associated with difficulties in oxygen supply and prevention of hyperchamoniaemia. The rest of the subchapters reflect in a logical sequence the fundamental quintessence of the problems of balancing energy and plastic metabolism, the functional adaptive significance of aerobic and anaerobic training, the productivity and quality of recuperative sleep, its phases for somatic and cognitive-emotional recreation. Particular attention is paid to the significance of sensorimotor

integration, stimulation of somatosensory reflexes and modern trends in the development of rural and urban design and construction.

The study informs us about the methodological, technological and complex support of experimental modeling and systematized fundamental multifactorial laboratory testing of the organism's response to specific environmental, daily activity and nutritional conditions. The methodological approach is characterized by the complexity and combination of both experimental models and occupational conditions, respectively, and analytical laboratory work by combining techniques. Such combination is less common in research laboratories, as narrow specialization of laboratory analysis prevails, even if it is quite progressive. Research and development technology in the field of neuroprotection and neurorehabilitation requires close interdisciplinary collaboration and application of the latest advances in biomedical engineering.

Chapter 3. "NEUROPROTECTION AND NEUROREHABILITATION PROGRAM, RESULTS OF TESTING IT IN EXPERIMENTAL MODELS AND IN THE "PERSON-MEDIUM-PEER-PEERFORMANCE" MODEL"

It is an algorithm built conceptually and strategically into a program of purposeful actions, in which each of the 8 proposed Steps is subjected to experimental and laboratory tests to convincingly argue and highlight the complex mechanisms involved. Tested in sufficient depth, in particular the gas exchange stage, the sleep-wake cycle, the adaptability of aerobic fitness systems, strength qualities based on the accentuated remodeling of body tissues (nervous, skeletal muscular, cardiac muscular, blood vessel walls) as well as vascularization, sensorimotor integration and somatosensory proprioceptive stimulation, which underpin the training of professional skills and, lastly, the need for evolutionary and physiological justification of the design and construction of rural and urbanized environments, the development of 'therapeutic environment' concepts and technologies, particularly in therapeutic and rehabilitation centres.

Compartment **GENERAL CONCLUSIONS AND PRACTICAL RECOMMENDATIONS**

presents the underlying hypotheses and those derived from the findings, covering a systemic multifactorial complex through a variety of experimental modeling and laboratory tests, the application of which proves the need for urgent engineering involvement of high-precision, physiologically compatible measurement technologies that allow real-time observations. The findings reflect the diversity of molecular, cellular and tissue responses to specific environmental and experimental exposures as well as to daily activity patterns in combination with diet. Practical recommendations address the urgent need for implementation, particularly in educational, therapeutic, rehabilitation and recreational settings as well as in occupational safety.

BIBLIOGRAPHY includes the 497 sources cited in the thesis.

The ANNEXES compartment contains tables and figures, reflecting the results obtained, copies of patents, innovator certificates, implementation acts and participation in various scientific events.

THESIS CONTENT

1. JUSTIFICATION OF THE URGENT NEED TO DEVELOP A NEUROPROTECTION AND NEUROREHABILITATION PROGRAM TO MAINTAIN THE CAPACITY OF HUMAN RESOURCES (SITUATION ANALYSIS IN THE FIELD OF THE THESIS)

Advanced NASA research methods provide convincing evidence of an annual increase in the concentration of CO_2, CO and other toxic gases in the atmosphere in combination with a decrease in atmospheric, ocean and inland groundwater oxygenation. The combination of oxygen deficiency with an excess of carbon dioxide proves to be a powerful disruptive factor, potentially capable of inducing adaptation, distress, pathology and death [12]. Adaptation to hypoxia leads to increased oxygen saturation during the resting period by facilitating function, including and through induction of neuroglobin (*NGB*) synthesis in brain formations [7]. *NGB* and cytoglobin (*Cygb*), which play different roles in maintaining brain viability under hypoxic or postischemic conditions. Both the induction of *NGB* and *Cygb* biosynthesis and their neuroprotective effect provide a pronounced tolerance to exposure to natural environmental hypoxia [2, 8, 18]. The rapid reinduction of brain-derived neurotrophic factor (*BDNF*) biosynthesis by secondary aerobic training suggests that primary training ensures the formation of neuroplastic memory initiated by prior induction of *BDNF* expression [27]. The cAMP response element binding protein (*CREB*) is important for spatial orientation, successful spatial learning and probably plays a certain role in the process of ensuring the resistance of neurons to the conditions of a possible stroke. Aerobic and strength (anaerobic) training through the neurotrophic action of *BDNF* stimulates the onset of neuroregenerative processes, including the formation of new neurons (neurogenesis).

Existing state programs point to the solution, determining the importance of nutrition and combining it with daily activity training. On a global scale the World Food Program operates, which provides for the mandatory provision of a balanced and adequate diet for the population of different ages [1]. Refusal of a targeted policy of "*Healthy Eating*" leads to serious negative consequences for the socio-economic status of the country, its socio-economic status, work capacity and protection [11, 20, 35]. There are several hypotheses about the restorative and repair function of sleep. Periods of sleep are necessary for the induction and maintenance of mechanisms that ensure neuronal plasticity of the control centers of the nervous system [6]. The role of sleep in promoting neuroplasticity may be multifaceted and include the processes of triggering and maintaining gene expression of functionally significant factors, as well as the reactivation of neuronal assemblies during post-training sleep [16, 28, 36]. The course of the internal biological clock depends strictly on periodicity signals from the external environment. Such signals are called "*zeitgebers*" (from German "*zeitgeber*" – "*giving of time*") [29]. The daily lighting regime, social factors, food intake, alternation of work and recreation play the role of zeitgebers [5, 21, 38]. The behavioral and physiological reactions of animal organism in experimental models are similar to those observed in workers and employees on night shifts and under unfavorable environmental conditions [30]. Women with different occupations who work night shifts are at potential risk of breast cancer [4, 10, 14]. A significant increase in the risk of breast tissue carcinogenesis is observed among nurses, who perform night shift and round-the-clock *on-call* duties [31, 32]. Exposure to artificial lighting at night is officially considered an occupational carcinogenic potential based on the decrease in melatonin levels, when they should be at their peak [34]. Disturbances of the sleep-wake circadian biorhythm and, in particular, harmful changes in sleep structure and quality contribute to stroke, myocardial infarction, metabolic syndrome and oncogenesis [9, 25].

Overtraining induces a reduction in the limits of adaptability and protection due to the onset of fatigue. The consequences of central fatigue allow the use of, for example, electroencephalography (EEG) and its subsequent spectral analysis by analyzing so-called DC potentials (*omega* waves). Periodically repeated monitoring (screening) makes it possible to follow the development of adaptive processes triggered by the applied training in order to correct the individual adaptation program [3]. People, who perform military service, are often exposed to extreme environmental factors and are forced to adapt to them. For example, heat stress, which occurs when performing professional duties in extreme temperature and humidity conditions, is a constant acute problem for military personnel [26]. The use of herbal adaptogenic preparations helps increase work productivity and survivability under extreme environmental conditions. Adaptogenic action aims not to block the stress response, but to attenuate it in order to prevent depletion of the endocrine secretory apparatus. Adaptogens have a protective effect on testosterone biosynthesis mechanisms, facilitating adaptation to stressful conditions. The adaptogenic effect of the active component salidroside (2-(hydroxyphenyl)ethyl beta-D-glucopyranoside) from *Rhodiola rosea* extract ("*golden root*") has been detected. This active ingredient is known to be a protective agent of erythrocytes against oxidative stress. *Rhodiola rosea* is known to inhibit the growth and development of cancer cells. Functional activity of the thyroid gland and the production of triiodothyronine, tetraiodothyronine are induced when using an extract from the plant body Ashwagandha (*Withania somnifera*). The extract induces favorable changes in the contractile activity of the heart muscles and normalization of cholesterol levels, as well as maintenance of fertility and reproductive activity, hematopoiesis and functional state of the immune system, reducing convulsive initiation and clinical manifestation of seizures.

In an industrial and agricultural occupational setting workers are exposed to an increased risk of neurodegeneration and carcinogenesis because the environment is sometimes polluted with a wide variety of chemicals, including pesticides, raw materials, toxic solvents and inert carriers. Pesticides have been detected in all samples from large rivers with mixed agricultural and urban land use influences and *dev99* percent in samples from intraurban rivers [33]. The effects of environmental pesticide exposure on a range of neuropsychiatric disorders and neurodegenerative diseases such as Alzheimer disease (AD) and Parkinson disease (PD) [24]. The development of neuromodulation technology provides an increasingly targeted effect on nerve centers and in the delivery of pharmaceutical agents to target structures [23]. The discovery of these mechanisms is based on fundamental studies of the neuroplasticity and neurodegeneration of *DA*-ergic neurons and is urgently needed for the prevention, treatment and rehabilitation of PD. The hippocampal complex is one of the highly sensitive formations of the brain, which responds to environmental factors, daily individual activity and nutrition [1, 6]. Strategies that focus on strengthening the potential of human resources create the basis for economic innovation and the growth of Human Capital, which is crucial for the upswing of the national economy. There is a close relationship between environmental conditions in the workplace, Economic Performance and Sustainable Development. If the percentage loss of "*productive hours of work*" reduces annual GDP in all countries, then they will be summatively substantial [13, 17]. Therefore, there is an urgent need for technical sources to diagnose the earliest manifestations of functional disorders induced by degenerative processes. The acute socially and economically significant problem of preserving and increasing the working capacity of citizens, increasing labor productivity and ensuring the competitiveness of the finished product can sometimes be solved by resorting to unpopular methods. Bio-inspiration can shape all human production activities in an environmentally friendly and harmonious way. The formation of new Biological Systems opens absolutely new possibilities in the development of programs to correct, optimize and adapt daily human activities according to changing environmental conditions. Any form of behavior of a social individual is strongly influenced by

the environment created during everyday life: in the family, school, in a collective or work group, or in a public place. The urban planning technologies of the present and the future are characterized by the desire of the creators to harmonize with the surrounding environment [22]. In the Scandinavian countries, the planning of "*Zero Cities*" built by analogy with the production of zero waste, is relevant [37]. The network of "*Smart Cities*" are the next stages of the important objectives that will revolutionize our understanding of how to interact with the environment and modernized gadgets.

Therefore, the design and construction of rural and urban environments are rarely evolutionary and based on physiology, although there is a direction of development of "healing" and "sensory" architecture. The design and construction of the living space of the human population now and in the future should be based on the principle of maintaining the viability and regeneration of both ecosystems and their constituent elements, as well as the population factor.

2. MATERIALS AND METHODS

2.1 Selection of groups of experimental laboratory animals and individuals according to occupation, design of experiments and occupational models

In applied experimental models, mature laboratory animals (rats) raised in vivarium conditions with a standard diet and free access to water and natural light were used. The first applied model is "*Intermittent hypobaric hypoxia*", in which the laboratory animals in the experimental group (n=5) were previously adapted to the ambient environment in a hypobaric chamber. The reduced atmospheric pressure inside the chamber corresponded to an altitude of 2500 and 3000 m (moderate) and 5000 m (severe), i.e. hypobaric environment for 30 days with a daily exposure of 5 hours. The ascent to altitude was carried out in stages with stops of 5-10-15 minutes at altitudes of 1000; 2000; 3000; 4000 m equivalent to the atmospheric pressure of: 0.89; 0.78; 0.69; 0.61 (atm), correspondingly. The exposure time at a maximum altitude was gradually increased during the first 15 days (from 5 minutes to 5 hours).

The next experimental model "*Accident with the breathing apparatus*" simulated breathing through the rostral mask with the valve open and closed. This model also represents the simulation of the "*Obstructive Sleep Apnea*" model. For the experimental simulation of the impact of the combination of hypoxia/hypercapnia environmental factors on the body, the "*Hyperbaric Humid Environment*" model was developed and applied. A comparative analysis was performed between groups of non-adapted and pre-adapted to the environment of "*Intermittent hypobaric hypoxia*" before the start of the main experiment with the application of the "*Humid Hyperbaric Environment*" model. In another group, the animals followed an adaptation course according to the "*Preliminary aerobic training*" model. The aerobic training program was implemented by swimming daily for 40 days, with exposure from 300 to 1200 seconds (t_{water}=18-20ºC). The experimental model "*Adaptation to aerobic training*" with a duration of 28 days in volunteer student athletes (men, 19-22 years old, n=10) was applied thanks to the collaboration with the Faculty of Physical Culture and Sports. The program included mandatory monitoring of blood oxygen saturation (SpO_2), maximum consumption (VO_2max/kg) indirectly, glucose concentration, lipid profile and blood urea concentration. The adaptation program was based on aerobic training with intensity (75-80% of VO_2max), frequency (3-5 sessions/week) and session duration (30-90 min). The "*Strength training (anaerobic)*" model was also applied with the usual diet (n=5) and a diet rich in proteins combined with the consumption of a preparation of plant origin and adaptogenic action (n=5). Anthropometric tests included measurement of abdominal circumference (*AC*), chest circumference (*TC*) and calculation of the ratio of abdominal to chest circumference (*AC/TC*). The determination of body composition, especially the percentage of adipose and muscle tissue, was carried out manually by caliperometry with the help of a measuring device – digital

electronic caliper (*KEC-100-1-I-D TVES*). The combination of a protein-rich nutrition with a natural adaptogen was applied by consuming orally ground Goji berries (V=200 ml) (hanging buckthorn fruits, *Lycium Barbarum*, manufacturer "*Qingdao Sunfine Co., LTD, China*") at a dose of 21g per average body weight of 70 kg, i.e. 300 mg/kg of body weight daily for 40 days. As part of the project, a new "*Biologically Active Food Supplement*" (*SABA*) with antioxidant and adaptogenic action was developed and patented. The effects of *SABA* were tested in an animal model experiment. *SABA* in the amount of 50 mg (166.7 mg/kg) was administered orally mixed with food (3-4g) 40 min before the administration of the hydroethanolic solution (10%, V=1 ml). To study the influence of *SABA* on the duration of forced sleep, Diphenhydramine solution (1%, a chemical stress agent) was administered.

The experimental modeling of daily activity in laboratory animals was carried out with the application of the "*Night shift work*" model, based on forced activity in a rotating cage. The next experimental model promoted an "*Enriched Environment*" (*EE*) in laboratory animals (rats, *Rattus norvegicus*) and in wild marine mammals (nothern fur seal, *Callorhinus ursinus*), giving the animals more surrounding space. To apply the "*Enriched Environment*" model for wild animals, the chamber in which the animal was housed was filled with seawater (t_{water} = 15-17°C) so that navigation in the water was possible for 72 hours with a feeding schedule (morning 7:30-8:00 and evening 18:30-19:00). Importantly, strict waterproofing and integrity of the polygraphic recording device (recoder) was ensured. The model of "*Enriched environment*" in combination with "*Adaptation to aerobic training*" was also applied to volunteer individuals. The study was carried out anonymously on a contingent of practically healthy people (students of the Faculty of Physical Culture and Sport) (n=15) aged between 19 and 22 during the summer camp on the Dniester coast, the group of people examined regularly practiced various activities locomotor physical activity (walking, running, outdoor games) with a frequency of 3 to 5 times a week and a duration of about 90 minutes. Locomotor effort included moderate- and high-intensity exercise. To test the limitations of the locomotor activity performed, subjects were subjected to a high-intensity, high-volume task. Thus, we tested the design model of the "*River-Lake*" community for its effect of forming the favorable action of forest and aquatic environmental factors and safety conditions for the participants. Locomotor load included moderate- and high-intensity exercise. To test the limitation of the performed locomotor activity, the subjects were subjected to a high intensity (VO_2max>70%) and an increased load. Pulse oximetry (SpO2 measurement) is a relatively simple and technically easy to implement method for indicating the function of the gas exchange system in the body. An objective assessment of the functional state of the gas exchange system in the human body was also carried out using the functional tests of Stange and Genchi, based on testing the aerobic capacity of the body during breath holding (apnea). All individuals were tested for qualitative and quantitative evaluation of the expression of emotions when they are virtually "immersed" in an environment conditional on safety and health, as well as in a safety-threatening environment. Such testing was based on video monitoring or screening of the psychomotor reactions of the facial muscles of individuals during visual and auditory sensory perception. The Facial Action Coding System (*FACS*) is a methodology that allows us to classify and evaluate the mimic psychomotor reactions of a person with changes in his emotional state [3]. Each mimic psychomotor reaction is defined as a Motor Unit (*MU*) and a Motor Descriptor (*DM*). In the *FACS* arsenal there is a list of the main *MU* and *MD*, in which each receives its own code: *AU 16, AU 22*, etc. (*Action Unit, AU*).

2.2 Neurosurgical methodology for the implantation of chronic polysomnography electrodes based on the stereotaxic technique in animals

In our experimental model, we used sexually mature laboratory animals (rats) raised in a vivarium with a standard nutrition programt, with free access to water and natural light. Of exceptional importance were the studies in which we applied an experimental model on wild

mammals with a unique evolutionarily determined adaptation to life activity in aquatic environments, systematically using breath holding (apnea) and sensory observation during sleep against the background of unihemispheric sleep with slow waves (*Delta* sleep or nonREM sleep). Before the start of the experiment, all animals underwent surgery using a stereotaxic technique under general anesthesia by inhalation of a mixture of oxygen and isoflurane (3-4 %) and intraperitoneal injection of ketamine at a dose of 2-4 mg/kg. Neurosurgical intervention was performed to prepare laboratory animals (rats) and wild-type animals (*Callorhinus ursinus* and *Tursiops truncatus*) for electrophysiological recordings combined with video monitoring of daily activity in a specific environment. Wild type animals (*WT*) were kept in strictly standardized conditions of the dolphinarium, under the close supervision of experienced and accredited veterinarians (n=3). In cooperation with the Institute of Ecology and Evolution "A.N. Severtsov" of the Russian Academy of Sciences (Moscow), participation in the project to study the sleep characteristics of marine mammals at the Utriş Marine Biological Station (Novorossiisk) was carried out. The project director was the university professor, Dr. Jerome M. Siegel, and the head of the scientific unit was Dr. Oleg I. Lyamin (*University of California Los Angeles, UCLA, Department of Psychiatry, Semel Institute of Neuroscience and Human Behavior*) and Dr. Lev M. Mukhametov. It was this team of scientists in 1971-1972 who first discovered unihemispheric slow-wave sleep in dolphins based on the electroencephalogram (*EEG*). Laboratory animals (n=5) and wild-type animals (n=3) were implanted with electrodes to record the bioelectrical activity in the regions of the neocortex (*Electrocorticogram, ECoG*), of the CA1 field of the hippocampus (*Electrohippocampogram, EHpG*) to achieve the objective of testing the reactivity of cortical and hippocampal neurons to the specific environment. In order to correctly detect the onset of the REM sleep stage, the objectification and quantification of awakening, motor and behavioral reactivity, immersion electrodes were additionally chronically implanted to record the bioelectrical activity of the oculomotor muscles (*Electrooculogram, EOG*) and of the cervical muscles (*Electromyogram, EMG*) (Fig. 2.1). Recordings were amplified and digitized using the device (*Power1401/Micro1401 MkII*) with "*Spike 2 version 4*" software (*Life Sciences data acquisition & analysis system, Cambridge Electronic Design Limited, CED*).

After the post-operative recovery period, an environmental modeling experiment was started, characterized by the combination of hypoxia/hypercapnia (n=5), in which, with the help of a rostral mask equipped with a corrugated hose and a valve, breathing from atmosphere through a mask and breathing with a rebreather (no exhalation into the atmosphere) with a closed valve. During the development of the REM-sleep stage, there was breathing disturbance (dyspnea by closing the valve on the breathing tube) until awakening from sleep and hyperventilation. This experimental model represents the "Obstructive Sleep Apnea" simulator and was performed repeatedly, daily for 15 days. In addition, the methodology of awakening from non-REM sleep and REM sleep was evoked by applying an auditory sensory (sound) environmental signal through the natural threat vocalization of the rat (Rattus norvegicus) (n=5), and the nothern fur seal (*Callorhinus ursinus*) (n=2) of different intensities (50-60 dB). To estimate the arousal state, the relationship between the total power of the delta rhythm before and after the application of the sensory stimuli was calculated. Total power was determined over a period of ten periods of 3 seconds duration (totally 30 seconds).

The representation and spectral power of the rhythms (*alpha, beta, delta, theta*) in the ECoG recordings were calculated and all digital material was accumulated for further evaluation. ECoG and EHpG recording was performed according to a standard scheme. 6 derivations were used (Fig. 2.1).

In addition, wake latency, duration of slow wave recovery (delta activity), and magnitude of alertness-induced desynchronization were performed by maximizing each derivation (Fig. 2.2).

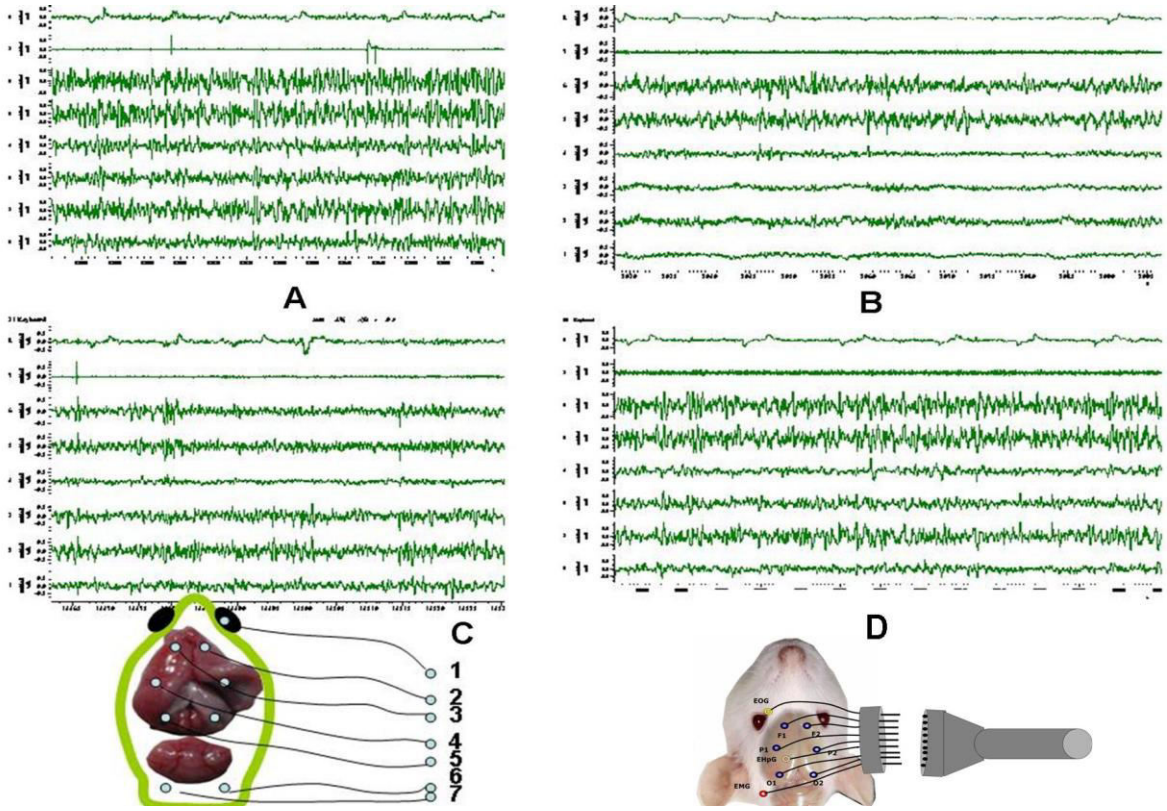


Figure 2.1. Polysomnograms obtained by non-stop recordings and the stereotaxic electrode implantation technique in wild (*Callorhinus ursinus*) and laboratory (*Rattus norvegicus*) mammals: A-bilateral non-REM sleep; B-unihemispheric non-REM sleep (right hemisphere); C-unihemispheric non-REM sleep (left hemisphere); D-regional asymmetry

We used derivations from the regions of the cerebral cortex: prefrontal, frontal, parietal, temporal and occipital, relative to each other. The principals were designated: F; P; and O (frontal; parietal; and occipital). The recording of ECoG and EHpG was performed in the following states: resting state of the subjects with eyes open; state of rest of the subjects with closed eyes; state of drowsiness and the stages (stages) of rest (restoration) sleep. In the available ECoG and EHpG, cross-correlation of the variability of the amplitude of bioelectric activity fluctuations in various interhemispheric and intrahemispheric derivations was also analyzed, using Pearson's "*r*" correlation coefficient. The intensity of artificial lighting in the surrounding environment was taken into account. A group of animals (n=5) exposed to the long-term influence of artificial light (LED, 15 Watt) was tested.

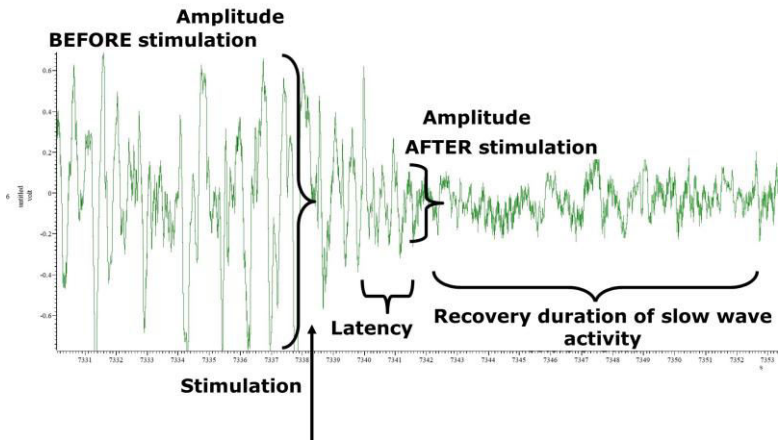


Figure 2.2. Maximized recording of EEG activity to measure response latency, amplitude, and duration to bimodal environmental cueing

2.3 Methods of evaluating psychomotor, somatosensory and somatomotor reflex activity in daily activity mode

Individuals practicing moderate locomotor physical activity (walking, running, outdoor games) with a frequency of about 3 times a week and with sessions lasting about 40-60 minutes. The objective evaluation of the degree of vulnerability of psychosomatic and psychovegetative interrelations and, in particular, of the respiratory system was obtained by monitoring during functional tests and the breath-holding test. Subjects were tested using spirometry (*MIR Spirobank spirometer, Medical International Research*), breath-holding test and real-time pulse oximetry (*Pulsox-300i pulse oximeter, Konica Minolta*). Psychosomatic interrelations were assessed by means of the somatosensory and somatomotor examination. Psychophysiological testing was based on video surveillance of the psychomotor reactions of individuals' facial muscles in response to multisensory input imitating a threatening social conflict situation. The neurological examination included the determination of the individual's sensory proprioceptive and motor reflex activity. Such a determination of physiological indices is complex and allows the assessment of somatosensory and somatomotor reflex activity, as well as the individual morphofunctional state of the musculoskeletal system. Qualitative and quantitative assessment of sensory reflex and proprioceptive motor activity began with general examination, posture, ability to maintain a straight upright position, standing and sitting. The individual was then asked to walk a distance of approximately 3 meters. Attention was paid to the coordination of walking, the absence of anomalies or difficulties in performing certain movements. Then, it was suggested to walk in a straight line, measuring the distance with your feet. The presence of swaying, the degree of balance and the uncertainty of placing the foot on the floor surface were noted. Balance was tested when standing on toes and heels. Afterwards, muscle tone was assessed in the upper and lower limbs in the sitting and supine positions. Tone was tested in the shoulder, forearm, hand, thigh, lower leg and plantar areas. A good muscle tone during the test is manifested as a sufficiently good musculotendinous resistance to the movement of a limb or part of it in the opposite direction. Further examination included determining the ability to maintain strong muscle tension in the limbs and trunk. Then the testing of somatosensory reflex activity was performed, which included the assessment of sensitivity in different areas of the skin surface of the body according to the somatotopic maps, first of all: to light superficial touch; secondly: to the superficial painful impact with a sharp object; thirdly: to vibrations. The level of segmental localization of the presumed lesion in the spinal joints or in the spinal nerve roots was determined by testing the somatosensory and somatomotor reflex activity according to the somatotopic representation of the different segments of the spinal cord on the individual's body.

2.4. Methodology for evaluating the neuromodulatory action of brain monoaminergic neurotransmitter systems using high-performance liquid chromatography (*HPLC*)

For fundamental analysis of the neuromodulation of *MA*-ergic neurotransmitter systems, high-performance liquid chromatography (*HPLC*) based on electrochemical detection (*ECD*) using a C18 (octadecyl) phase column (*HPLC* column, 150 mm x 4.6 mm , particle size 5 µm, *Agilent, USA*). The concentration of dopamine (*DA*), norepinephrine (*NE*), serotonin (5-hydroxytryptamine, *5-HT*) and their metabolites: 5-hydroxyindoleacetic acid (*5-HIAA*) and homovanillic acid (*HVA*) in nerve tissue homogenates from brain regions studied.

2.5. Evaluation of protein biosynthesis in neurons and neuroglial satellites based on histochemical analysis of the amount of nucleic acids in cellular compartments

Tissues were histochemically processed (fixation with Carnoy's liquid) and then embedded in paraffin. The amount of nucleic acids (*NA*) in neurons and their neuroglial satellites was

quantified by gallocyanine-alum chromic staining. The optical density (D_{NA}) was calculated using the transmission current (I_i) in the analyzed cell section and in the tissue-free section (I_0). Morphometric tests were performed by measuring the size of cell compartments (nucleus: karyon; nucleolus; body: soma) and calculating the volume of the cytoplasm (perikaryon). The preparations were digitized and densitometry of the stained reaction product (nucleic acids) in different cellular compartments was performed using the *Corel-Photo-Paint 12* program. Also, the volume (V) of each of the cellular compartments analyzed was calculated from micromorphometry using the formulas of the rotation ellipsoid ($V=\pi/6Dd^2$) and the triaxial ellipsoid ($V=\pi/6Dd\sqrt{Dd}$), where: V – the volume of the cell compartment (μm^3) D and d are the large and small diameters of each of the compartments.

2.6. Assessment of monoamine breakdown by the enzymatic activities of monoamine oxidase A and monoamine oxidase B and protein cleavage by the proteolytic activity of cathepsin D

The procedure for determining the activity of monoamine oxidase A (*MAO-A*) was based on the deamination reaction of serotonin, and that of determining monoamine oxidase B (*MAO-B*) on the deamination reaction of benzylamine. *MAO-A* and *MAO-B* were determined spectrophotometrically in basic medium at the wavelength λ_1=500 nm or λ_2=460 nm. In the microcentrifuge tubes of the biochemical analyzer "*FP-901*" (*Helsinki, Finland*) the research material (tissue homogenate, 0.05 ml) was measured with 0.2 ml phosphate buffer solution (0.04 M, pH 7.4) and serotonin solution 0.03 ml (10 mmol) (for *MAO A*) or benzylamine solution 10 mmol (for *MAO B*), shake and incubate for 60 min at t=37°C. For biochemical tests of cathepsin D activity, tissue samples were immediately placed in ethylene-diglycol-thiamide (*EDTA*) extraction solution with cold sucrose (t=4°C, pH 4.5) and were homogenized. The method used to determine the activity of cathepsin D is based on the ability of the enzyme to undergo intense hydrolysis of the hemoglobin macromolecule (*Hb*) with the formation of acid-soluble derivatives.

2.7. Application of biochemical methods to study carbohydrate and lipid metabolism in aerobic and anaerobic training

Peripheral blood lactic acid levels were also determined in real time using a portable lactate analyzer (*EKF Diagnostics Scout 4*). To perform the analysis on this analyzer, it is enough to draw a minimum volume of blood, which can be 0.5 µl. Glucose concentration was determined using a portable glucometer (*Bionime Rightest GM300*) with the same advantages as for lactate determination: real-time monitoring. Plasma concentrations of triglycerides (*TG*) and total cholesterol (*CT*), high density polyproteines (HDL-C) and low density polyproteines (LDL-C) were determined by the enzymatic method in the automatic analyzer (*Analyzer A15, BioSystem S.A., Spain*).

2.8. Applying the laws of statistical variation to determine the validity of the difference between studied groups

All numerical materials were statistically analyzed by ANOVA using the *t*-Student test. Also, a cross-correlation analysis of the bioelectric activity in different regions of the cerebral cortex was performed. All investigated biological parameters obeyed the law of normal distribution.

3. NEUROPROTECTION AND NEUROREHABILITATION PROGRAM, THE RESULTS OF TESTING IT IN THE EXPERIMENTAL MODEL AND IN THE "PERSON-ENVIRONMENT-OCCUPATION-PERFORMANCE" MODEL

3.1. Step 1 testing of the neuroprotection and neurorehabilitation program, ensuring sufficient functional gas exchange in the body

To achieve the proposed objectives, first of all, conceptually and strategically, the algorithm or Basic Steps of the Neuroprotection and Neurorehabilitation Program was developed. This program was systematized in the form of an algorithm of sequential actions built from 8 Steps presented by keywords (Fig. 3.1).

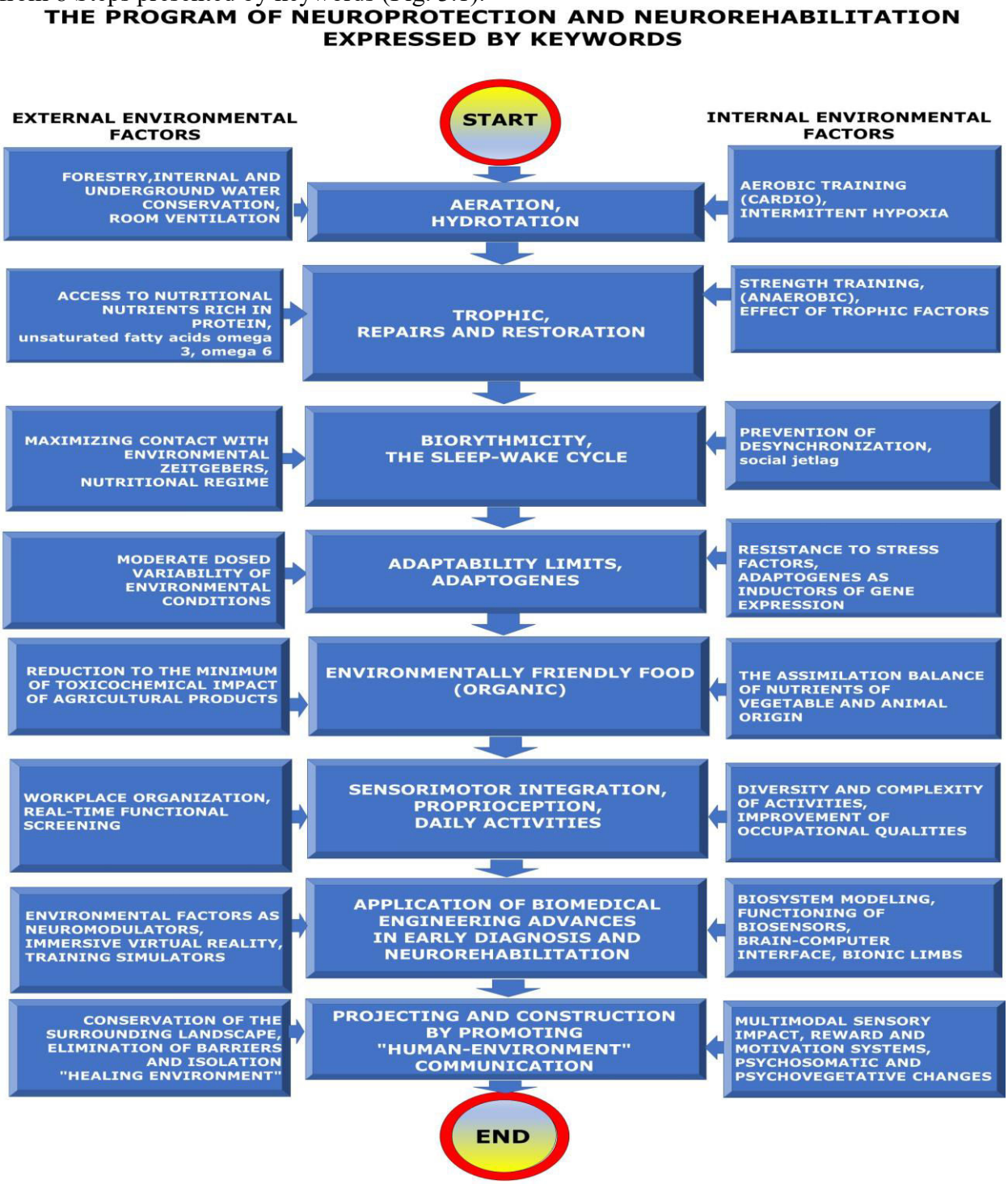


Figure 3.1. Schematic representation of the Neuroprotection and Neurorehabilitation Program in the form of an algorithm built from 8 Steps by keywords

The first such Steps - Step 1 is: "*Ensuring a functional and sufficient gas exchange in the human body*" or by keywords "*Aeration, Hydration*". Step 1 includes procedures to optimize gas exchange, both in the internal environment and in the external environment of the body. In the

internal environment we achieve this through aerobic training and adaptation to moderate intermittent hypoxia, and in the external environment by changing the partial pressure of oxygen ($PatmO_2$) and carbon dioxide ($PatmCO_2$) in the gas mixture from the atmosphere. The main objective was pursued – to experimentally stimulate the effect of the combination of hypoxia and hypercapnia on bioelectric neuronal activity in brain formations and to test the possibility of preventing their depressive effect with the help of prior aerobic training. To achieve this goal, the experimental model "*Intermittent hypobaric hypoxia*" and the model "*Accident with the breathing apparatus*" were applied.

During the implementation of the project, non-stop polysomnographic screening of the circadian sleep-wake cycle was performed in wild animals. The spectral analysis of polygraphic electrophysiological recordings and their synchronization with the video monitoring of daily animal activity allowed the evaluation of interhemispheric and intrahemispheric asymmetry in conditions of forced desynchronosis (sleep deprivation) through communicative sound sensory signals. In wild animals the sea bear (*Callorhinus ursinus*) and dolphins (*Tursiops truncatus*) were investigated the evolutionary adaptation mechanisms of the circadian sleep-wake cycle to specific conditions of the aquatic and underwater environment. It is remarkable that this way of adapting brain activity and neuroprotection is characterized by the highest degree of interhemispheric asymmetry during unihemispheric or unilateral slow-wave sleep (*Delta* sleep or non-REM sleep). The evolutionary determinism of the emergence of unihemispheric slow-wave sleep demonstrates the excellent neuroplastic and neuroprotective capacities and flexibility of the mammalian animal brain, which prevent the processes of neurodegeneration and cerebral blood circulation disorders. Hyperventilation reactions were recorded during video monitoring of dolphins (*Tursiops truncatus*) in dolphinarium conditions (n=1) in sleep and wakefulness during surface swimming and underwater diving. It is remarkable that the reaction expressed by hyperventilation was recorded in accordance with a certain biorhythmicity [the cycle time was 40 min (2400 s)] when the animal suddenly came to the surface from under water. This response is similar to the response to sleep apnea in experimental animals and humans with obstructive sleep apnea (*OSA*). It is known that during the stage of REM sleep in the homeostasis of the body, the so-called "*Vegetative Storm*" occurs, characterized by a sudden jump in the functional activity of the respiratory and circulatory systems against the background of cervical muscle atony and rapid eye movements, manifested in characteristically by *EMG* and *EOG*.

Respiratory functionality and balanced gas exchange are the main objects of modern research. The main objective was pursued – to experimentally stimulate the effect of the combination of hypoxia and hypercapnia on the bioelectric neuronal activity of the brain formations and to test the possibility of preventing their depressive effect by the help of aerobic training. The "*Preliminary aerobic training*" model allows the discovery of neuroprotection mechanisms achieved by facilitating the maintenance of the spectral power of the *beta-alpha* rhythms in the neocortical areas and the *theta* rhythm in the hippocampus. Spectral analysis of *ECoG* and *EHpG* recordings demonstrated that the combined effect of hypoxia/hypercapnia leads to a significant reduction in the spectral power of the *beta* rhythm in *ECoG* (cu 47,3%, $P<0,05$). The expression of the alpha rhythm is reduced in the occipital regions in the animal at rest (recreation). Theta rhythm indicators, coming from the entorhinal cortex, increased significantly, while those of hippocampal origin showed a tendency towards reduction. After the application of the "*Preliminary aerobic training*" model, the *beta* and *alpha* rhythms remained unchanged compared to the preliminary recordings and were significantly higher compared to the untrained animals (by 26.7%, $P<0.05$ and 33.8, respectively %). The application of the "*Accident with the breathing apparatus*" model leads to an increase in the frequency of occurrence and spectral power of the theta rhythm of hippocampal origin in animals pre-adapted to "*Preliminary aerobic training*" compared to non-adapted animals. The characteristic reduction of *beta* and *alpha* rhythms was reversed and the spectral power of the hippocampal *theta* rhythm

increased after aerobic training. Aerobic pretraining has been shown to have the ability to maintain sufficient spectral power of *beta* and *alpha* rhythms in the neocortex fields, as well as the *theta* rhythm in the hippocampus. The application of this experimental model allowed the manifestation of the adaptogenic action of the "*Preliminary aerobic training*" Program on the neural apparatus of the cortical and hippocampal areas. Promoting bioelectrical activity in the hippocampus and *theta* rhythm can improve neuroplastic remodeling [39].

After the first day of sleep during the rest period (from 8:00 AM to 5:00 PM) interrupted by wakefulness episodes due to the "*Accident with the breathing apparatus*" model in association with bioelectrical changes, a statistically significant increase in the concentration of serotonin (*5-HT*) was observed in the area of the respiratory motor center (*NTS* or *Sol*) compared to the control group (534.0 ± 27.2 vs 439.0 ± 23.4 pg/mg of wet tissue, P < 0.05) (Fig. 3.2 A).

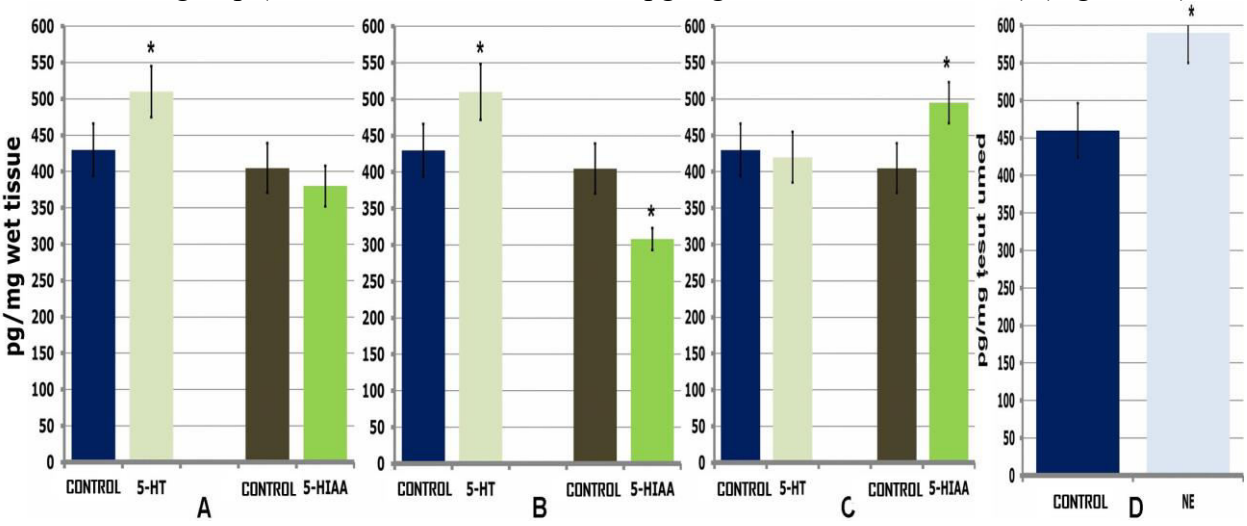


Figure 3.2. Serotonin turnover in the dorsal respiratory group of the brainstem (*NTS*) after the first day of "*Accident with the breathing apparatus*" and after 15 days on the background of adaptation to intermittent hypoxia in the area of the dorsal raphe nucleus (*DRd*), the concentration of norepinephrine in the locus coeruleus (*LC*) (*5-HT*; *5-HIAA*; *NE*, pg/mg wet tissue)

In animals adapted to intermittent hypoxia, after 15 days of performing the "*Accident with the breathing apparatus*" model, the concentration of *5-HT* increases against the background of the decrease in the concentration of 5-HIAA in the localization area of the locus coeruleus (*LC*) compared with the group of unadapted animals (Fig. 3.2.B).

După perioada timp 15 zile de realizare a modelului „*Accident cu aparatul de respiraţie*" a fost evidențiată o creștere a concentrației de *5-HIAA* (Fig. 3.2 C) în zona nucleului rafe dorsal (*DRd*) (494,0±19,1 față de 407,0±17,6) și NE în zona de localizare a *LC* (573,0±23,5 față de 463,0±21,4 pg/mg) (Fig. 3.2 D). A fost depistată şi o prelungire semnificativă statistic a perioadei latente de trezire.

During the adaptation to the "*Intermittent hypobaric hypoxia*" model in the paraventricular nucleus of the hypothalamus (*Pa*) an increase in the relative number of neurons with reduced Q_{NA} in the nucleus (karyon) was highlighted. Against this background, Q_{NA} in the cytoplasm (perikaryon) was significantly increased by 26.9% (P<0.01). In the nucleolus of neurons in Pa Q_{NA} exceeded the level of the control group by 24.7% (P<0.05) (Fig. 3.3).

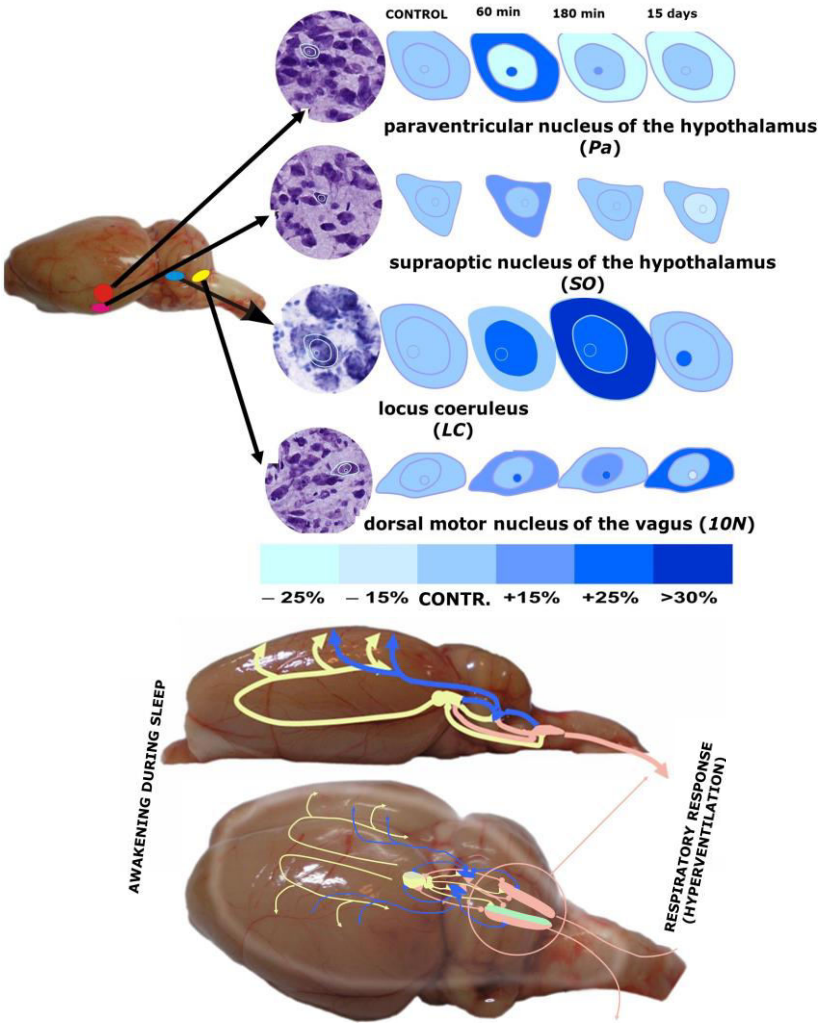


Figure 3.3. Reactions of the protein biosynthesis apparatus of neurons in brain centers according to changes in the amount of nucleic acids (Q_{NA}) in cellular compartments, scheme of the mechanism of awakening to hypoxic/hypercapnic stimulation during sleep

After 1 hour (60 min) of hypoxic influence Q_{NA} in the nucleus of neurons increased by 24.2% in the *NE*-ergic *LC* center ($P<0.05$). After 3 hours (180 min) of hypoxic influence, a significant decrease in Q_{NA} was found by 22.4% ($P<0.05$) in the cytoplasm of the neurons in *Pa*, and in the neurons of the supraoptic nucleus (*SO*) it returned to the level of the control group. Although, after the 180 min period, Q_{NA} also increased in the perikaryon of neurons in the *NE*-ergic *LC* center by 39.1% ($P<0.01$) (Fig. 3.3) in association with a significant increase in volume. After exposure to intermittent hypoxia for 15 days, the response of neurons in the dorsal vagal nucleus (*10N*) is late and prolonged, than in *Pa* and the *NE*-ergic *LC* center. Adaptation to the "*Intermittent hypobaric hypoxia*" model for 15 days is characterized by signs of exhaustion of the cellular apparatus of protein biosynthesis in neurons of the paraventricular nucleus of the hypothalamus (Fig. 3.3).

Enzymatic activity of *MAO-B*, which manifests the decomposition of monoamines, is reduced in the region of the anterior hypothalamus. The proteolytic enzyme activity in the region of the *5-HT*-ergic center of the raphe nuclei (*DR*) after hypoxic influence for 15 days was below the level of the control group by 26.4% ($P<0.01$). *MAO-A* activity is suppressed in the *5-HT*-ergic center *DR*.

Therefore, adaptation to "*Intermittent hypobaric hypoxia*" contributes to maintaining a sufficient level in the terminals of *5-HT*-ergic neurons in the *NTS* respiratory center by reducing

serotonin degradation. The bidirectional neuromodulatory connection is probably enhanced in the "*Locus coeruleus-Hypothalamus*" direction and is supported by the suppression of monoamine degradation in the hypothalamic nuclei. Hypoxic influence facilitates modulation of *5-HT*-ergic center *DR* neurons and promotes inhibition of cathepsin D and *MAO-A* activity in this brain region.

Importantly, priliminary adaptation to aerobic physical activity during the first 3 days led to an increase in the relative proportion of cells with increased Q_{NA} amount in both the sensorimotor cortex and the respiratory motor center and reached 156% (P<0, 05) and 143% (P <0.05) respectively, compared to the control group (Fig. 3.4). The results of densitometry of the stained product in neurons indicate that the amount of Q_{NA} per cell in the pyramidal neurons of the sensorimotor cortex increased after a 3-day loading by 39.3% (P<0.01) compared to the control group. In neurons of the respiratory motor center, Q_{NA} per cell increased by 23.4% (P<0.05) (Fig. 3.4). Importantly, the amount of Q_{NA} per cell increased statistically significantly as well, but was more pronounced in motor respiratory center neurons: by 28.6% (P<0.01) compared to the control level.

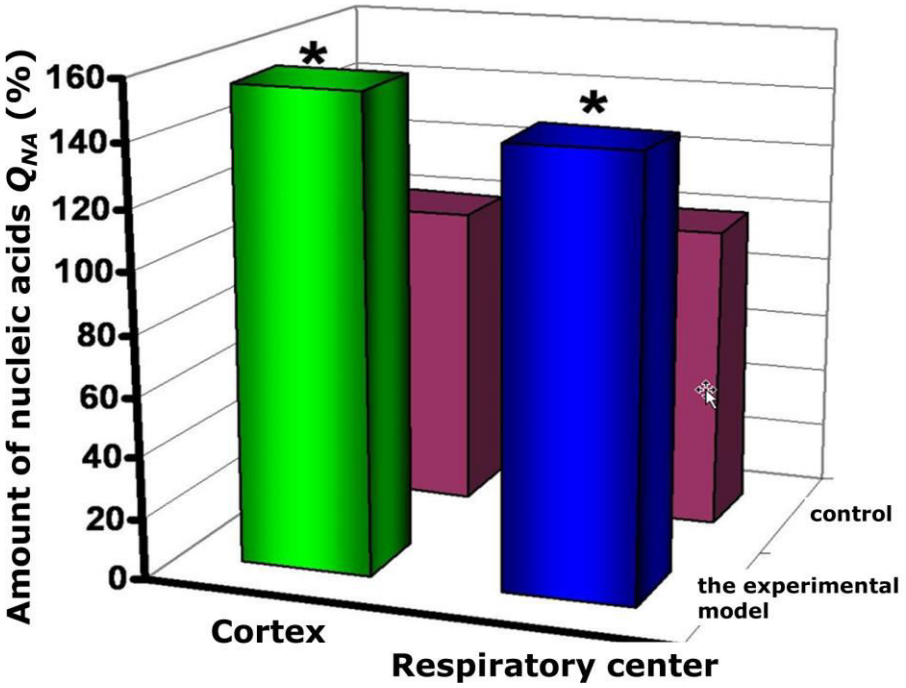


Figure 3.4. The amount of nucleic acids (Q_{NA}) in brain centers after 3 days of daily aerobic physical activity

A comparison of the results obtained on animals pre-adapted and non-adapted to "*Preliminary aerobic training*" exposed to underwater diving in "*Humid Hyperbaric Environment*" with the application of the "*Simulator*" is very demonstrative. In pre-adapted animals the increase in the amount of Q_{NA} per cell, namely in neurons of the respiratory motor center, was significantly lower by 17.3% (P<0.05) than in non-adapted animals. However, the increase in the amount of Q_{NA} per cell in the pyramidal neurons of the sensorimotor cortex in the adapted animals was 26.7% (P<0.05) higher than in the non-adapted group of animals after they completed the experiment with the application of the "*Humid Hyperbaric Environment*".

The relative proportion of cells with increased amount of Q_{NA} in adapted animals exceeded that in non-adapted animals in pyramidal neurons of the sensorimotor neocortex. In another series of histochemical analyses, a comparison of pre-adapted and non-adapted animals through the "*Preliminary aerobic training*" model showed that after aerobic training both in adapted and non-adapted animals the proportion of cells with increased Q_{NA} quantity was increased in the center motor respirator.

Moreover, the results obtained in laboratory animals (rats) demonstrated that the percentage of neurons with increased Q_{AN} amount predominates in the lateral area of the hypothalamus (*LHA*) and the ventral tegmental area (*VTA*) in animals adapted to the combination of "*Preliminary aerobic training*" and "*Intermittent hypobaric hypoxia*" (Fig. 3.5). The ratio of neurons with optical density and the amount of Q_{NA} per cell reduced, average and increased after the adaptation program to "*Preliminary aerobic training*" shifts towards the predominance of neurons with optical density and the amount of Q_{NA} increased.

The personalized neuroprotection and neurorehabilitation program can promote neuroplasticity changes in the *OX*-ergic activation system centered in the *LHA* and the *DA*-ergic reward system in the *VTA* and nucleus accumbens (*NAcc*) by balancing the activation and reward systems, energy metabolism and plasticity (Fig. 3.5).

Determinations of optical density (D_{NA}) and amount of nucleic acids (Q_{NA}) per cell compartment volume (*Vn*; *Vnl*; *Vcyt* and *Vsom*, nucleus, nucleolus, cytoplasm, and soma, respectively) showed that the "*Accident with the breathing apparatus*" model causes a significant reduction of Q_{NA} in both nucleus and cytoplasm of *5-HT*-ergic center *DR* neurons by 19.8% and 22.5% ($P<0.05$ and $P<0.01$, respectively) relative to control values.

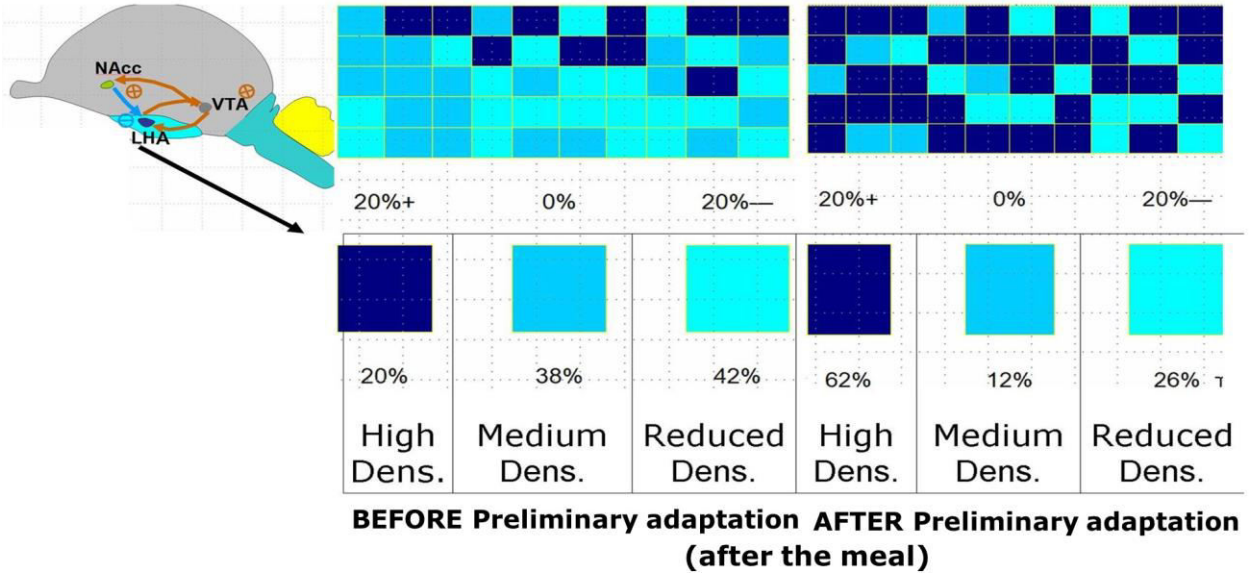


Figure 3.5. Redistribution and percentage of neurons with high, medium and low optical density in the lateral hypothalamic area (*LHA*), involved in the connection with the ventral tegmental area (*VTA*) and the nucleus accumbens (*NAcc*)

An increase in Q_{NA} was observed only in the nucleolus of neurons up to 122.3% ($P<0.05$) compared to control animals. Changes in neuroplasticity, assessed by Q_{NA} measurements for the entire cell body of neuroglial satellite cells, are characterized by an increase in the number of neuroglial satellite cells up to 129.7% ($P<0.05$) against the background of neuronal weakening. In the nuclei of neurons from the population in the *NTS* or *Sol* dorsal respiratory group, the Q_{NA} value was reduced by 33.4% ($P<0.05$) compared to the control. At the same time, a high value of Q_{NA} 118.4% and 123.3% respectively ($P<0.05$) is preserved in the nucleolus and cytoplasm of neurons in *Sol*, as well as it has a tendency towards reduction in neuroglial satellites. Significant reduction of Q_{NA} in neuronal nuclei may mean that the process of transcription and synthesis of new RNA molecules is suspended. The low level of Q_{NA} in the cytoplasm, probably ribosomal RNA (rRNA), clearly proves the weakening of protein synthesis activity in these cells.

Therefore, the increase in the representation of cells with increased amount of Q_{NA} was detected in the sensorimotor cortex during hypoxic action and may be characteristic for the periodic exposure of the organism to the environment, in which repeated episodes of "*Intermittent hypobaric hypoxia*" alternate with periods of "*normobaric normoxia*". This

experimental model is a hypoxic training simulator for aircraft pilots, climbers and performance athletes.

3.2. Testing Step 2 of the neuroprotection and neurorehabilitation program, which ensures that the limits of neuroplasticity are extended by optimizing daily activity and diet

Thanks to the collaboration with the team of the Faculty of Physical Culture and Sport, a study was carried out on practically healthy student-athletes who completed the "*Adaptation to aerobic training*" Program lasting 28 days. As a result, it was found that after a period of 28 days of carrying out the personalized adaptation program, the individual anaerobic threshold increases significantly due to the increase in the degree of oxygen saturation in the blood (SpO_2). What was highlighted by the Genchi functional test.

It is supposed to improve the body's aerobic capacity and indirectly energy metabolism. The obtained results allow the assumption that by applying such individual programs "*Adaptation to aerobic training*" it is possible to prevent the imbalance of carbohydrate, lipid and protein metabolism. The lipidogram towards the end of the "*Adaptation to aerobic training*" Program showed an increase in *HDL-C* (from 30.1±3.4 to 44.9±5.1 mg/dL, $P<0.01$) and a decrease in *LDL-C* (from 30.4±0.8 to 19.3±0.2 mg/dL, $P<0.01$). After the implementation of the "*Adaptation to aerobic training*" Program, a veridical attenuation of the increase in urea concentration in the blood was observed immediately after the end of the last training session, which suggests that the ratio between protein degradation and their assembly deviated in the direction of the activation of anabolic processes. Various training and didactic programs implemented in summer camps must necessarily include screening of O_2 consumption, CO_2 emissions and SpO_2. SpO_2 measured in the recovery state after performing the "*Adaptation to aerobic training*" Program was favored from 93.1±0.6 to 97.9±0.2% ($P<0.05$) compared to the pre-adaptation period. Therefore, the program of outdoor recreation and development activities in a forest park area, practiced during summer camp tours in the form of active locomotor activity, favors the development of gas exchange processes in the body.

The implementation of the "*Adaptation to strength (anaerobic) training*" Program was accompanied by a reduction in the weight of adipose tissue from 11.56±0.98 to 10.11±0.98 kg ($P<0.05$) and the increase muscle mass from 66.75±1.13 kg to 68.18±0.98 kg ($P<0.05$), i.e. adipose tissue constituted 14.8±1.1% (before the program) and 12.9±1.1% (after the program); muscle mass 85.2±4.3% (before the program) and 87.1±4.3% (after the program). The change in lipid profile revealed an increase in *HDL-C* concentration from 33.4±3.3 to 47.6±4.8 mg/dL ($P<0.05$) on the background of a reduction in *LDL-C* from 37.6 ±1.7 mg/dL to 25.3±1.3 mg/dL ($P<0.001$) after completing the program. The "*Adaptation to strength (anaerobic) training*" program ensures the balancing of energy and plastic metabolism, the deviation of the ratio between fat and muscle mass towards the predominance of the latter and to weaken the lipotoxicity of adipose tissue, which also affects carcinogenesis processes. The spread of muscle and motor weakness in the human population, the predominance of the proportion of adipose tissue over muscle in the body composition is becoming widespread, especially in the physically inactive population. The predominance of a sedentary lifestyle among pupils, students, intellectual workers and employees is obvious.

3.3. Testing Step 3 of the neuroprotection and neurorehabilitation program, which aims to extend the limits of neuroplasticity by balancing circadian rhythms

In the prefrontal cortex (*PFC*) of animals after forced daily activity through the "*Night shift work*" model during motor activity during rest (sleep), the concentration of *NE* increases significantly by 36.7% ($P<0.01$) compared to animals from the control group. The increase in 5-*HT* concentration in the prefrontal and motor cortex after forced exercise was less pronounced but statistically significant by 17.9% ($P<0.05$) and was associated with a decrease in *DA* concentration by 23.2 % ($P<0.05$). It is important to note that the concentration of *HVA*, which is

a metabolite of DA, increases by 21.8% (P<0.05) when modeling forced daily activity during the rest period. In order to optimize motor activity during the rest period, its duration was shortened to 240 min and combined with eating with hedonic food consumption. Optimizarea a făcut posibilă detectarea unei creșteri semnificative a concentrației de *DA* cu 27,5% (P<0,01) în zona *PFC*, în comparație cu animalele care au fost forțate să stea active de 2 ori mai mult (480 min) și fără aportul de alimente hedonice. Optimizarea a relevat şi o creştere a nivelului de 5-HT în hipocampul pe fondul micşorării concentraţiei de *5-HIAA*. Aşadar, optimizarea activităţii zilnice a promovat reducere semnificativă a raportul *5-HIAA/5-HT*, ceea ce indică o atenuare a descompunerii a serotoninei. Central MA-ergic neurotransmitter systems are key players in the fine-tuning mechanisms of adaptive motor activity under changing environmental conditions. Daily activity, characterized by forced wakefulness during the recreation period, excessively activates the *NE*-ergic system and suppresses the *DA*-ergic one, which provides the effect of consolidation and mobilization against the background of the attenuation of motivation. The optimization allows for the leveling of the imbalance created by the centripetal neuromodulatory action on the neocortex and hippocampus. The increase in the frequency of episodes of awakening from sleep leads to unwanted fragmentation of the entire period of sleep, deterioration of the quality, quantity of sleep and, consequently, a weakening of neuroplastic transformations. Awakening during non-REM sleep and REM sleep is symmetrical and more pronounced in ECoG, but awakening is regionally different, i.e. asymmetric, during shallow and delta-dominant sleep. The expression of awakening from sleep in ECoG is characterized by the reduction (desynchronization) of the delta rhythm in the frontal-parietal-occipital direction. The awakening threshold is higher during REM sleep compared to shallow sleep and deep non-REM sleep in the same hemisphere. Latency is prolonged and the duration of alertness, on the contrary, is reduced during deep non-REM sleep. Inhibition of sensory input from the environment is more pronounced during REM sleep. The general negative impact of desynchronosis caused by night shift work on neuroplasticity is manifested by a decrease in work capacity and productivity, a deterioration in concentration, a decrease in the level of alertness (vigilance). The implementation of the program is also inspired by the Global Strategy for the development, creation and strengthening of human resources described in the documents of the Summit "*Workforce 2030*".

From a conceptual, strategic point of view, the Neuroprotection and Neurorehabilitation Program provides some basic principles for favoring "*Environment-Organism*" or "*Environment-Human*" communication and the neuromodulatory action of natural environmental factors induced by it in various ways. For the formation and estimation of the common indicators of this communication, the following are decisive: the presence/absence of communicability that creates a state of mutual satisfaction; the presence/absence of communicative aggression that creates social discomfort, it is especially important to understand that communication is determined not only by communication between people (interpersonal), but also by communication between people and the external environment.

For the practical application of the Neuroprotection and Neurorehabilitation Program, we propose tests based on the natural or virtual immersion of individuals in the modeled environment and the recording of the synchronized polygram of psychosomatic and psycho-vegetative reactivity that is expressed through EEG and EMG bioelectrical changes, as well as activity fluctuations respiratory systems, blood circulation and cardiac activity. Such experiments were carried out by imitating the adaptogenic and stressogenic environment accompanied by recordings of ECoG and EMG reactions. Data obtained from experimental tests and spectral analysis demonstrate that sound stimulation and subsequent awakening during deep slow-wave sleep (delta or nonREM sleep) and REM sleep is symmetrical and more pronounced than awakening from shallow sleep, when the response is different at the level regional, i.e. asymmetric (Fig. 3.6). Characteristic changes found in EMG recordings confirmed this

observation by demonstrating the behavioral motor response to auditory stimulation that disrupts sleep phases (Fig. 3.7).

The expression of awakening from sleep in the ECoG is characterized by the reduction (desynchronization) of the *delta* rhythm in the frontal-parietal-occipital direction. Importantly, the awakening threshold is higher during REM sleep compared to superficial *Delta* sleep (non-REM sleep) and even deep *Delta* sleep in the same hemisphere (Fig. 3.8). Latency is prolonged, and the duration of alertness, on the contrary, is reduced during deep *Delta* sleep. We assume that during REM sleep the sensory inhibition of sensory input from the environment is expressed.

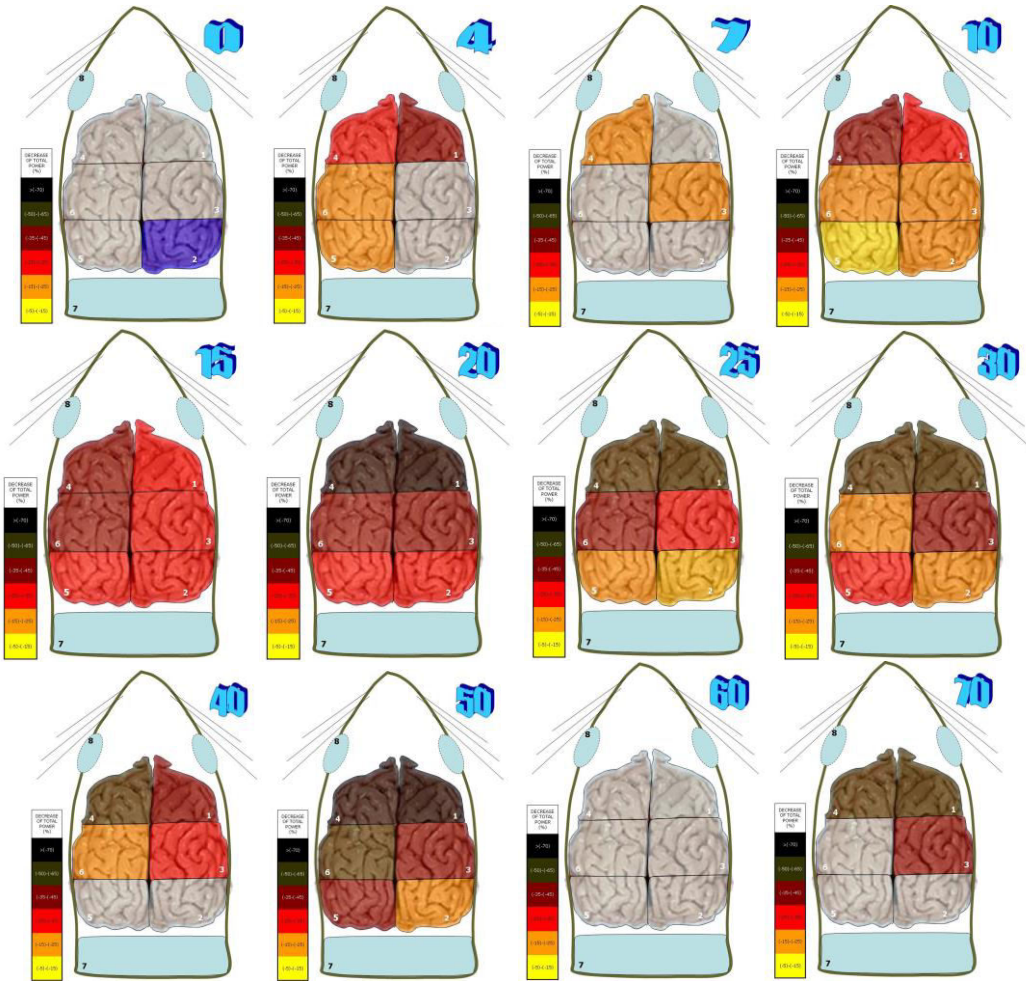


Figure 3.6 Mapping severity of awakening from unihemispheric and bilateral slow-wave sleep as a function of sensory stimulus intensity

The survival of the living organism depends largely on the ability of the animal or human to maintain an adequate level of alertness, as well as its ability to dynamically adjust emotional state according to physiological demands and changing environmental conditions. Environmental factors that can be considered extreme: hypoxia and hypercapnia; heat and cold can alter an individual's mental and physical functioning.

These observations suggest the idea that inhibition of sensory input has a neuroprotective effect during the consolidation of working memory and, in particular, spatial memory, so decisive for navigation in the surrounding space. Bimodal or multimodal signaling during the "*Environment-Organism*" interaction may be the most appropriate neuromodulator and trigger of adaptive neuroplastic remodeling in nervous, neuroendocrine and endocrine regulatory centers.

It is worth noting that acclimatization, adaptation to acceptable environmental conditions is based on a neuromodulatory effect. The activation states of the cerebral cortex allow increasing

the capacity to process information from the external environment. For the successful implementation of the Neuroprotection and Neurorehabilitation Program, it is extremely important to ensure strict adherence to the daily schedule of work, services and educational activities.

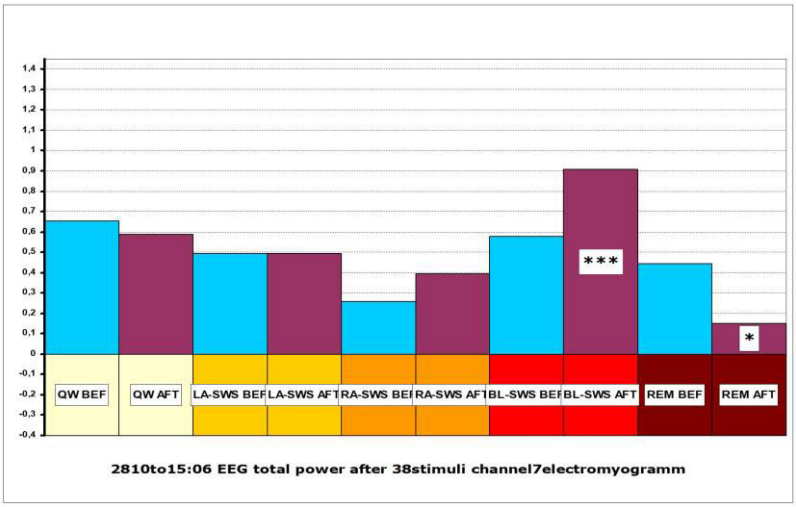


Figure 3.7 Quantitative expression of synchronization in EMG during slow wave sleep (nonREM) and beta rhythm in REM sleep and wakefulness in channel 7 (electromyogram) QW BEF – wake before stimulus; QW AFT – awake after stimulus; REM BEF – REM sleep before the stimulus; REM AFT – REM sleep after stimulus; LA-SWS BEF – unihemispheric delta sleep (left hemisphere) before the stimulus; LA-SWS AFT – unihemispheric delta sleep (left hemisphere) after stimulus; RA-SWS BEF – unihemispheric delta sleep (right hemisphere) before the stimulus; RA-SWS AFT – unihemispheric delta sleep (right hemisphere) after stimulus; BL-SWS BEF – bilateral delta sleep before the stimulus; BL-SWS AFT – bilateral post-stimulus delta sleep

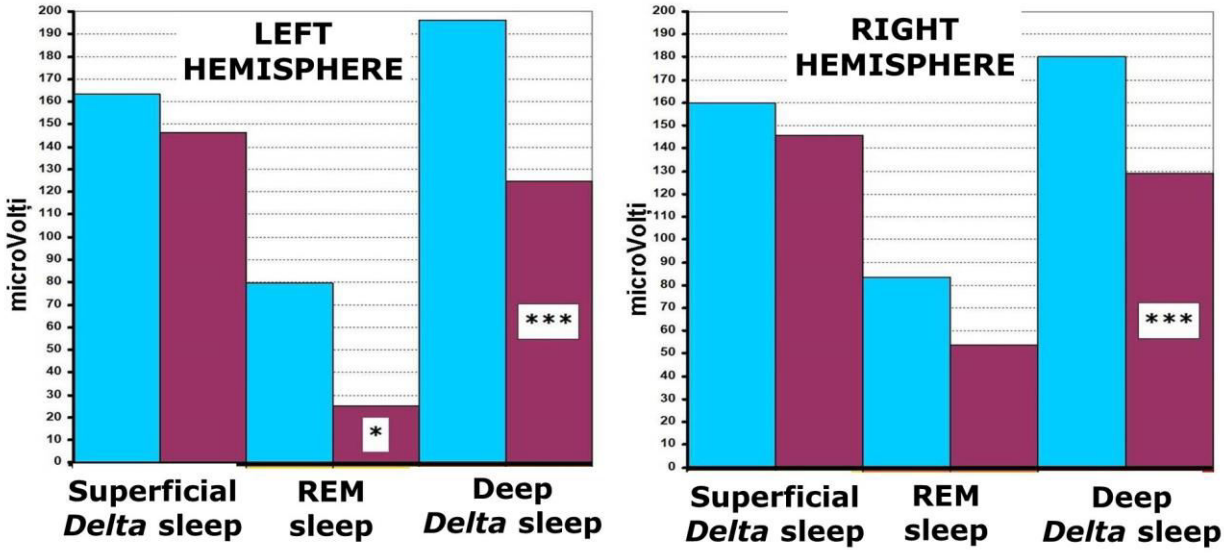


Figure 3.8 Mean delta amplitude of EEG activity at different sleep stages during awakening hyperventilation due to environmental hypoxic/hypercapnic signaling

Mental and physical abilities throughout the wake-sleep cycle, indicators of the functional state of respiratory and circulatory activity, neuroendocrine and immune systems, the dynamics of body temperature variation, as well as the nature of the body's response to certain pharmaceutical preparations present a strict daily biorhythm. The existence of such a biological rhythm is evolutionary, genetically determined and physiologically conditioned, therefore, a gross phase shift (desynchronosis) often leads to serious consequences.

3.4. Testing Step 4 of the neuroprotection and neurorehabilitation program, characterized by the inclusion of plant-derived adaptogens in the daily nutrition

The neuroprotection and neurorehabilitation program is designed to ensure the proper and optimal coordination of the interactions between two systems: the integral system of the body and the ecosystem of its environment, fundamentally based on the concept of "*General Adaptation Syndrome, GAS*" [Hans Selye, 1936] . This systematic approach integrates almost all functional systems of the body into a single whole with the surrounding environment. Integration, in turn, is achieved due to the coordinated interaction of the upper parts of the brain: the cerebral cortex, the formations of the limbic system, the nuclei of the thalamus, the reticular formation, as well as the centers of the brain stem: the dorsal raphe nuclei (*nucleus raphe dorsalis, DRd*), *locus coeruleus (LC)*, *ventral tegmental area (VTA)*. Both higher neuroregulatory centers and trunk centers maintain bilateral functional connections with parts of the hypothalamus.

The obtained results show that in the Purkinje cells of the cerebellar cortex a vestibular (gravitational) effort lasting 36 hours caused a reduction in the amount of *NA* (Q_{NA}) in the nucleus (caryon) by 17.6% ($P<0.05$) and with 21.4% ($P<0.01$) in the cytoplasm (perikaryon). The morphometric index (volume) of Purkinje cell cytoplasm after gravitational exercise was reduced compared to preload values (Fig. 3.9). The mosaic of the distribution of protein biosynthetic activity in the processing centers of the brain at the macro level clearly demonstrates that the gravitational load induces a weakening of the biosynthetic capacities in the Purkinje cells of the cerebellar cortex. Since the combination of vestibular loading with swimming determines the maintenance of biosynthesis in the cerebellum and its consolidation in the brain stem center of the *5-HT*-ergic neurotransmitter system: *nucleus raphe dorsalis (DRd)*. It is assumed that the gravitational effort applied in the experimental model has adverse consequences at the level of the neuron-neuroglia system. However, reducing the volume of the cytoplasm (perikaryon) can also have a compensatory and neuroprotective value for maintaining the intracellular concentration of macromolecules. A statistically significant increase in Purkinje cell volume by 18.7% ($P<0.05$) was detected after a 7-day swimming exercise program (session duration 1200 s, t_{water} = 20-22°C), also associated with an increase in the total amount of neuroplasmic *NA* by 21.3% ($P<0.01$) against the background of a slight reduction in the amount of Q_{NA} in the nuclei of neuroglial cells (Fig. 3.9).

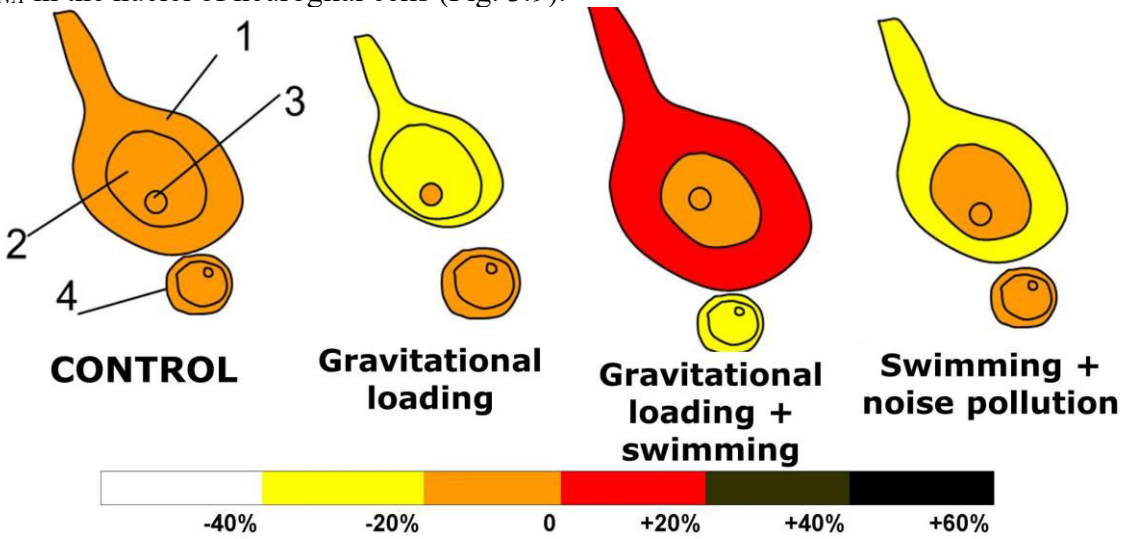


Figure 3.9. Changes in the quantity of nucleic acids (Q_{NA}) in cellular compartments of Purkinje cells in the cerebellar cortex: 1 – the perikaryon; 2 – the caryon; 3 – the nucleolus; 4- the neuroglial satellite

The obtained results showed that during the recreation period according to the experimental model "*Night shift work*", carried out acutely (for 36 hours without interruption) in

the hippocampus, the enzymatic activity of *MAO A* is suddenly reduced by 43% (P<0.05), which ensures the breakdown of the serotonin neurotransmitter (5-hydroxytryptamine, *5-HT*) in the *5-HT*-ergic terminals. So, during recreation after prolonged forced daily activity, the action of inhibiting *MAO A* activity occurs, which can serve as an indicator of the antidepressant effect of total sleep deprivation. In addition, intermittent moderate psychoemotional eustress induces *5-HT* release. This inductive effect on the *5-HT*-ergic center is crucial for mitigating the negative impact of distress on the emotional state and adaptive behavior and can be referred to as neuroprotective for the formations of the hippocampal complex.

The "*Adaptation to aerobic training*" model, in combination with an optimized diet and implemented in daily activity, is characterized by an increase in heart rate variability (*HRV*) and the index of the *LF/HF* ratio (Low Frequency/High Frequency). The *LF/HF* ratio demonstrates an improvement in the balance between the sympathetic and parasympathetic systems (sympatho-vagal balance) until the completion of aerobic training combined with optimized nutrition. This improvement in balance manifests as increased parasympathetic influences, allowing for more efficient recovery. The influence of the parasympathetic component of the autonomic nervous system is associated with an increase in the spectral power of the high-frequency (*HF*) range, the *LF/HF* ratio tends to decrease with the development of physical adaptation. For an objective qualitative and quantitative evaluation of adaptive and maladaptive reactions it is good to combine *EEG* with *HRV*. The "*Adaptation to Aerobic Training*" program promotes an increase in the level of adaptation in association with changes in the *LF/HF* ratio that are graphically manifested in the so-called "*green*" zone. The "*green*" zone is an aerobic zone that reflects a fairly high level of gas exchange and energy exchange, while the maximum oxygen consumption VO_2max reaches the limits: 75-85%. The spectral analysis of *HRV* serves as an informative indicator of the comparability of a personalized adaptation program to a response model. Food supplement with neuroprotective and adaptogenic effect represents a complex composition of ingredients. The composition includes biomaterials from: Amaranth (*Amaranthus L.*); Wormwood (*Artemisia absinthium L.*); Dihydroquercetin (*Larix sibirica L.*); Walnut (*Juglans regia L.*); Dandelion (*Taraxacum officinale L.*); Griffonia (*Griffonia simplicifolia L.*); Cornflower (*Glycyrrhiza glabra L.*); Rhodiola (*Rhodiola rosea L.*); Basil (*Ocinum basilicum L.*); Sage (*Salviae L.*), Rosemary (*Rosmarinius officinalis L.*). The first series of experiments demonstrated that the duration of sleep in animals from the intervention group was 55.2±5.1 min, and the duration of sleep in animals from the control group was 75.8±5.4 min during the time period of 180 min from 9:00 to 12:00 hours. The use of SABA promoted an average reduction of 27.2% (P<0.05) in the duration of sleep occurring following the administration of the 10% hydroethanolic solution. Rezultate obţinute probabil caracterizează efectul tonifiant al *SABA* asupra centrilor sistemului nervos central. În seria a doua a experimentului s-a constatat, că durata somnului animalelor din lotul de intervenție a constituit 115,6±6,7 min, dar la animale din lotul martor durata sumară a somnului a constituit 150,9±7,1 min. Administrarea SABA a promovat şi o reducere în medie cu 23,4% (P<0,01) duratei somnului survenit în urma administrării soluției de Diphenhydramine 1%. It is assumed that chemical stress causes the inhibition of the examined indicator, evidence of disturbances in the nervous system of experimental animals. Therefore, neuroprotection and neurorehabilitation programs must necessarily include a set of measures that induce and maintain the body's adaptation mechanisms to the environment. Seabuckthorn, also widespread in our region (*Lycium hulimifolium* is a synonym of *Lycium barbarum L. 1973*), is still different and widely known for the adaptogenic properties of Goji berries (from the Chinese *Níngxià gǒuqǐ*). Their adaptogenic, immunostimulating, anticancer effect is due to the rich content of antioxidants, vitamins from groups A, B, E, C, amino acids and essential minerals, which optimize gas exchange, blood circulation, energy consumption in conditions of lack of nutrients to meet the increased demand for energy [34]. Experimental tests of the effect of combining training with the

adaptogen were carried out in individuals who had normal physical development, without deviations from morphological and physiological norms. Changes in body composition were analyzed, using the caliperometric method, in 3 different groups of individuals who performed: 1 – aerobic training with regular nutrition; 2 – strength training (anaerobic) with regular nutrition; 2 – anaerobic training in combination with a protein-rich diet and the use of an adaptogen (*Lýcium bárbarum/Lycium chinense* fruit extract). Goji fruit extract is rich in vitamin P, which belongs to the group of plant polyphenols (bioflavonoids) and combines three biologically active substances: hesperidin, rutin and quercetin. The percentage of adipose tissue was reduced after the aerobic training program for 28 days. Body mass index decreased from 24.6±0.8 to 22.1±1.4. După antrenament anaerobic combinat cu dieta bogată în proteine și consumarea adaptogenului, dimpotrivă, indicele de masă corporală a crescut de la 24,4±1,1 la 24,9±1,5. The rate of adipose tissue decreased and muscle mass increased. In individuals exposed to the "*Anaerobic training combined with optimized nutrition*" program, the concentration of urea in the blood was before the start of the training session - 3.3±0.6 mmol/l and 60 min after the last session – 6.5±0.8 mmol/l. At the end of the "*Anaerobic training combined with optimized nutrition*" program, the last training session showed a less pronounced increase in urea concentration (from 2.8±0.3 mmol/l to 5.2±0.5 mmol/l). At the beginning of the "*Anaerobic training combined with optimized nutrition*" program during the first session, the estimation of the lactate concentration showed that the lactate threshold (the second anaerobic threshold) appears at the concentration of 4.2±0.5 mmol/l, after which the level of lactate increases up to 8.3±0.14 mmol/l. Lactate threshold during the last session at the end of the program was less pronounced, the postthreshold jump in lactate level was from 1.70±0.2 to 5.7±0.22 mmol/L ($P< 0.05$). Before the program post-session recovery was less significant (from 8.3±0.14 to 4.45±0.5 mmol/L). In the period after the completion of the sessions, recovery showed a significant reduction (from 5.7±0.2 to 1.85±0.6 mmol/L) within 20 min. In the dynamics of the aerobic training session (treadmill running for 30 min at the individually selected speed, which is equivalent to the intensity of 70% of VO_2max) the glucose concentration first increased slightly and then decreased from 4.14±0.19 up to 4.30±0.10 and 3.43±0.10 mmol/L). At the end of the program during the training session (intensity of 70% VO_2max) the initial increase in glucose concentration was more significant and the decrease is less pronounced than before the program from 4.19±0.15 to 4.48 ±0.16 and 3.98±0.14 mmol/L. Immediately after the session, the lipid profile showed that the implementation of the aerobic training program promoted a significant increase in *HDL-C* concentration from 30.1±3.4 to 44.9±5.1 mg/dL ($P<0.01$). The implementation of the program also contributed to a decrease in the *LDL-C* level from 30.4±0.8 to 19.3±0.2 mg/dL ($P<0.01$).

3.5. Conceptual elaboration of Step 5 of the neuroprotection and neurorehabilitation program, based on the inclusion of organic agricultural products in the daily nutrition

No segment of the population is fully protected from pesticide exposure, and the consequences have the potential to seriously damage neuroprotection mechanisms. Importantly, in regions with increased use of pesticides, compared to those with less use, the prevalence rates and risks of Alzheimer (*AD*) and Parkinson (*PD*) diseases [19, 24]. The consumption of agricultural food produced with the use of pesticides causes the risk of developing neurodegenerative transformations in nerve formations, increasing the incidence of certain diseases and decreasing human performance in the general population. The genesis of both neurodegenerative diseases *AD* and *PD* has not been fully elucidated and several exogenous (environmental) and endogenous (genetic) factors contribute to the occurrence and/or development of these diseases, which underlines the need to expand research on the identification of environmental risk factors. In the Neuroprotection, Neurorehabilitation Program it is necessary to take into account the fact that the etiology of neurodegenerative diseases is

multifactorial and potential external factors, including daily activity and toxicochemical exposures, are related to the risk of neurodegeneration. For productive screening, the concentration of *miRNA* can serve as a biomarker for the early diagnosis of *AD*. The association of specific *miRNA*s for some genes involved in *PD*, such as *SNCA* and *LRRK2* (coding for *leucine-rich repeat kinase 2*), has already been demonstrated. The Neuroprotection and Neurorehabilitation Program in cases of possible exposure to pesticides requires the use of these biomarkers to ensure effective screening and early diagnosis of neurodegeneration. Modern technologies for agricultural food production are forced to resort to artificial fertilizers, plant and animal protection products, and also significantly disrupt ecosystems. The destruction of landscapes and natural ecosystems is also caused by deforestation and the development of areas intended for agricultural land. One of the striking examples of combining ecosystem conservation and organic fertilizer production is peatlands, which are wetland terrestrial ecosystems where the bog prevents complete decomposition of plant material. The natural production of organic matter exceeds its decomposition, ensuring a net accumulation of peat. On the territory of Moldova, between the Prut and the Dniester, this natural heritage is located in the Stefan Voda district ("*Togai*" Swamp) and is managed by the "*Tighina*" Forestry Enterprise. Peat vegetation consists mainly of sphagnum moss, sedges and shrubs, which are the main building material for its production. Currently, the use, for example, of peatlands allows the economic development and profitability of the various sectors of Agriculture, Horticulture, Forestry. About 84% of the world's peatlands are believed to be in a natural or near-natural ecosystem state. Conceptually and strategically, the modernization of agricultural development should be carried out based on the restoration of ecosystems and the production of ecological food products. The entire territory of Historical Moldavia, the Carpathians, the central part of the Codriri of the Central Moldavian Plateau, the northern part of the Podolia Plateau, the southern regions of the historical Bessarabian lakes, the wetlands of the Danube Delta and the Lower Dniester are represented by unique natural landscapes, which any cost must not only be preserved, but also ensure their restoration.

3.6. Step 6 testing of the neuroprotection and neurorehabilitation program, including balance and sensorimotor integration

Through the implementation of the Neuroprotection and Neurorehabilitation Program we attempt to achieve neuromodulation of proprioceptive sensory reflexogenic activity by intentionally modifying the cumulative ascending sensory influx of impulses from specialized mechanoreceptors rushing to sensory processing centers. The entire receptor apparatus consisting of these mechanoreceptors is distributed in muscles, skin, tendons and ligaments, as well as in joint capsules. In the experimental model "*Night shift work*" in laboratory animals, the estimation of the degree of interhemispheric symmetry by cross-correlation analysis and the calculation of the asymmetry coefficient in the *ECoG* recordings showed an asymmetry formation effect. It is assumed, the increase in the degree of asymmetry is caused by bilateral interhemispheric disintegration. The significant increase in the amplitude and frequency of individual oscillations in the frontal and central-parietal derivations, which we discovered, may indicate the manifestation of the modulation of the activating systems of the brain. In particular, the orexinergic (*OX*-ergic) activation system of hypothalamic origin and the reticular system of the brainstem. The *OX*-ergic system, in turn, is known to modulate the major *MA*-ergic systems of the brainstem and the acetylcholinergic (*ACh*-ergic) system of the basal forebrain [479]. It is known that the etiology and pathogenesis of Alzheimer disease is dependent, especially on the activity of the *ACh*-ergic system. Testing of the *15-day Stimulation/Sensory Deprivation* Model demonstrated that test subjects maintain a positive emotional state during virtual immersion in a safe environment in the morning after a night's sleep. Facial psychomotor reactions demonstrated the predominance of facial movements in the area of muscle localization: *m. zygomatic major*

and *m. buccinator* (up to 130 and 120%, respectively) in contrast to background measurements in the same individuals. In the background estimates, the predominant psychomotor reactions were manifested in the muscle localization area: *corrugator supercilii* and *orbicularis oculi*. In cases of central fatigue it is necessary to eliminate the monotony and constraint of sensory input and/or perform intermittent sensory deprivation. In the Neuroprotection and Neurorehabilitation Program from a strategic point of view, it is important to optimize the regime of work, service, educational activities for the effective prevention of overload and fatigue, as well as ensuring the formation of a balance between stimulation and circadian sensory deprivation in combination with activities that improve the architecture and sleep quality. In addition to the sensory overload commensurate with working in an uncomfortable and motionless position, the sensory effort of the proprioceptive apparatus increases. Balancing sensory stimulation/deprivation is proposed as the main measure to prevent mental fatigue. The neuroprotection and neurorehabilitation program is focused, first of all, on sensory proprioceptive functionality, generated by the body's internal forces during positioning or locomotion in the environment. The program also includes neuromodulation of sensory reflexogenic activity by intentionally modifying the ascending sensory input. The neuroprotection and neurorehabilitation program takes into account the fact that compensation and repair processes in the intervertebral joints are slow. The increase in ascending sensory flow induced by proprioceptive exercises allows for the strengthening of recovery and repair capacities. Therefore, the appropriate plastic remodeling of sensory pathways, sensory and motor neurons, as well as muscle tissue is intentionally modulated by the Neuroprotection and Neurorehabilitation Program based on (anaerobic) physical strength training. Importantly, ascending sensory impulses from proprioceptors are always transmitted to the segmental and suprasegmental level, even from unexcited muscles.

The successful implementation of the Neuroprotection and Neurorehabilitation Program requires systematic monitoring, which, like the natural physiological proprioceptive apparatus, differentially tracks the smallest changes in the state of muscles, tendons, joints (static indicators), as well as movement speed, i.e. changes in dynamic characteristics. The implementation of the Program, first of all, ensures the strengthening of the fine coordination of movements that is impossible without the development of secondary sensory fibers. It is of vital importance that kinesthetic sensorimotor integration allows orientation and spatial locomotion in strict accordance with visual sensory information, which is the result of distance measurement to objects in the environment. The auditory (sound) and visual (lighting) sensory flow perceived by the sensory systems literally bombards the analyzing centers (processor), bringing not only informative communication signals, but also physical stimuli that create noise, and are by-products of technology, development devoid of content informative. In the lumbar region, where the pain often radiates, the lumbosacral inclination angle was significantly higher in the middle-aged group. In each of the disks: L1 and L2; L3 and L4; and L5, there is a significant decrease in the angle between the ventral and dorsal height of the intervertebral discs of the lumbar spine. The accumulated load causes an increase in the imbalance between the intensity, the level of adaptation and the degree of compensation and the probability of destructive degenerative transformations of the tissues. The neuroprotection and neurorehabilitation program, based on proprioceptive training, ensures the increase in the degree of supply to the intervertebral discs due to the diffusion induced by the increase in motor (rotational) torque in the joint. The application of programs is highly requested in Educational Institutions and must be based on a postulate that the system of coordinating the emotional state and behavior of adolescents is extremely complex and easily deteriorates, at the same time it is very difficult to correct and rehabilitate.

Conceptually, based on the review and synthesis, we propose that during the performance of work duties, when individuals are involved in constant interaction with a personal computer (PC), the characteristics of the monitor must be selected appropriately, the working time must be

strictly dosed, and the position of the eyes and the angle of concentration of the views must be adjusted. In addition to the sensory overload of the visual analyzer, when working in an uncomfortable and motionless position, the sensory effort on the proprioceptive apparatus also increases. For example, the position of the trunk, head and neck, characterized by lifting the chin up, tilting the head, pushing the upper part of the body forward or to the side, often occurs when the workplace is not organized correctly. When performing work duties in an uncomfortable position, the feeling of discomfort, signaled by the proprioceptive sensory system increases, as well as increases the risk of occupational disorders of the musculoskeletal system. Identifying early signs of mental, sensory and physical fatigue during educational, work and service activities can be done using methods of recording eye movements ("*eye tracking*"), providing objective information about the degree of focus of attention, the presence of motivation and of interest, as well as demonstrating the interests of the areas based on the results of the oculomotor activity trajectory. Multimodal environmental factors have a strong neuromodulatory effect, potentially able to intensify compensatory and reparative processes in tissues.

The quality of lighting and its nature (natural or artificial) are decisive for preventing accidents and ensuring productivity. The results of the EEG analysis show that intensive lighting through the visual sensory apparatus affects the level of vigilance of individuals. On the contrary, to ensure high-quality restorative sleep, complete darkness and silence is needed, i.e. of sensory deprivation. Sensory input associated with daily activity can cause a degree of interhemispheric asymmetry in the EEG recorded during sleep. The results of spectrometry of the spectral power of alpha, beta, delta and theta rhythms in ECoG recordings in wild animals in the case of photostimulation before sleep revealed the formation of asymmetry, which is manifested in the sleep spindles recorded during shallow sleep and sleep in the spindle stage. It is assumed that this asymmetry is determined to some extent by the lateralization of *NE*-ergic nerve terminals in the thalamic nuclei. It is known that the epicenter of the generation of sleep spindles is located in the thalamocortical system, which includes the nuclei of the thalamus and the sensory processing centers of the cerebral cortex. Fluctuations in another frequency range in ECoG recorded during sleep also show persistent asymmetry in the right hemisphere during non-REM sleep and in the left hemisphere during REM sleep. These oscillations correspond to the high *delta/theta* band (0.5-4/4-8 Hz). In support of this, an hourly predominance of delta waves in the right hemisphere during non-REM sleep has been identified. In addition to the discovery of these naturally occurring asymmetries in ECoG during sleep, attempts have been made to induce interhemispheric asymmetries through experimental manipulation with the application of visual sensory stimulation. An experimental model inducing ECoG asymmetry can be based on unilateral sensory stimulation. Such sensory stimulation is visual stimulation and sound stimulation shortly before sleep onset, as well as during non-REM sleep and REM sleep.

The implementation of the Neuroprotection and Neurorehabilitation Program is based on ensuring timely and productive restorative sleep after daily activity at work and at home. A common problem in the functioning of the mechanisms that initiate and maintain sleep cycles is falling asleep and waking suddenly from sleep, which interrupts the cycle, prevents the transition from non-REM sleep to REM sleep, and the completion of the sleep cycle. The structure of sleep is characterized by its fragmentation. This increased arousal and wakefulness during rest sleep may be due to increased activity of the *NE*-ergic neurotransmitter system. The results obtained demonstrate that the relative frequency of *alpha* rhythm episodes increases as the animal calms down and relaxes, as expected. It was found that the episodes of *alpha* rhythm at the beginning of the polysomnogram recording, i.e. when the animal has not yet passed to a sufficiently quiet state of wakefulness, they are found scattered in all derivations with a predominance in the frontal lobes (Fig. 3.10 A). Then, as they calm down with their eyes closed, they spread to the parietal and occipital lobes, beginning to predominate clearly in the occipital regions (Fig. 3.10 B). The frequency and spectral power of the *alpha* rhythm in the occipital areas in the baseline

and subsequent ECoG recordings were assessed. As shown by spectral analysis and manual calculations, the predominance of the *alpha* rhythm in the occipital areas differed significantly both in terms of relative frequency of episodes and in amplitude, depending on the duration of the recording and previous daily activity: habitual or associated with stimulations visual and sound sensors, which cause overwork and general fatigue. On average, *alpha* rhythm indices decreased in polysomnographic recordings by 18% ($P<0.05$). After daily activity associated with photostimulation and sound stimulation the presence of *alpha* rhythm in the occipital regions was significantly reduced when they were in a state of rest (quiet wakefulness) with eyes closed (Fig. 3.10 C). For the implementation of the Neuroprotection and Neurorehabilitation Program, it is important to detect a significant imbalance or a predominance of asymmetry in the frontal lobes in terms of the spectral power of the *alpha* rhythm.

The environmental factors visual (photostimulation) and sound (natural threatening roar of the animal) had a significant influence on the severity of the negative emotions experienced in terms of volume or intensity. This emotional state was associated with a reduction in the representation of *alpha* rhythm episodes by 45.3% ($P<0.05$) compared to the previous period without visual and sound stimuli. Moreover, the degree of desynchronization of the *delta* rhythm, i.e. the reduction of the average amplitude of ECoG oscillations, at the time of awakening from bilateral non-REM sleep, was 21.2% ($P<0.05$) more expressed in stimulated animals than in the previous period without bimodal sensory stimulation.

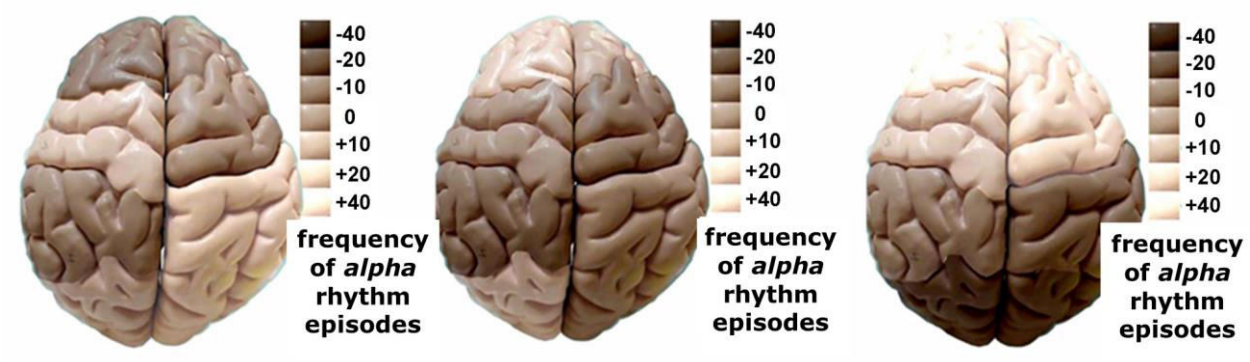


Figure 3.10 Shift of the area of *alpha* rhythm predominance to the occipital region:
A – state of rest (illumination); B – state of rest (without lighting); C – state of rest (without lighting, eyes closed)

Predominance of asymmetry occurred in the area of the prefrontal cortex (mean r value ranged from 0.003 to 0.068, $P<0.05$). The obtained data indicate that the environmental conditions associated with sensory stimulation have a characteristic effect on the state of health and the quality of sleep, especially on the level of awakening from sleep and the degree of its fragmentation. The polysomnogram data indicate a possible increase in the degree of anxiety in accordance with the increase in the asymmetry of the *alpha* rhythm in the area of the prefrontal lobe, with difficulties in the process of falling asleep (increased latency to fall asleep) and maintaining the cyclicity of sleep. It is evident that the environmental conditions associated with increased exposure to visual and sound stimulation significantly alter the quality of sleep, the level of arousal and the degree of sleep fragmentation.

It is assumed that daily activity has a significant impact on subsequent sleep architecture and the degree of sleep fragmentation.

The diurnal activity associated with multimodal sensory stimulation during the waking period is also accompanied by a rebound of the theta rhythm in subsequent sleep observed in the lateral areas of the central area of the cortex in the left hemisphere compared to the right hemisphere (Fig. 3.11 A and Fig. 3.11 B). The data show that visual stimulation, especially through the application of artificial lighting causes the formation of asymmetry, both interhemispheric and regional.

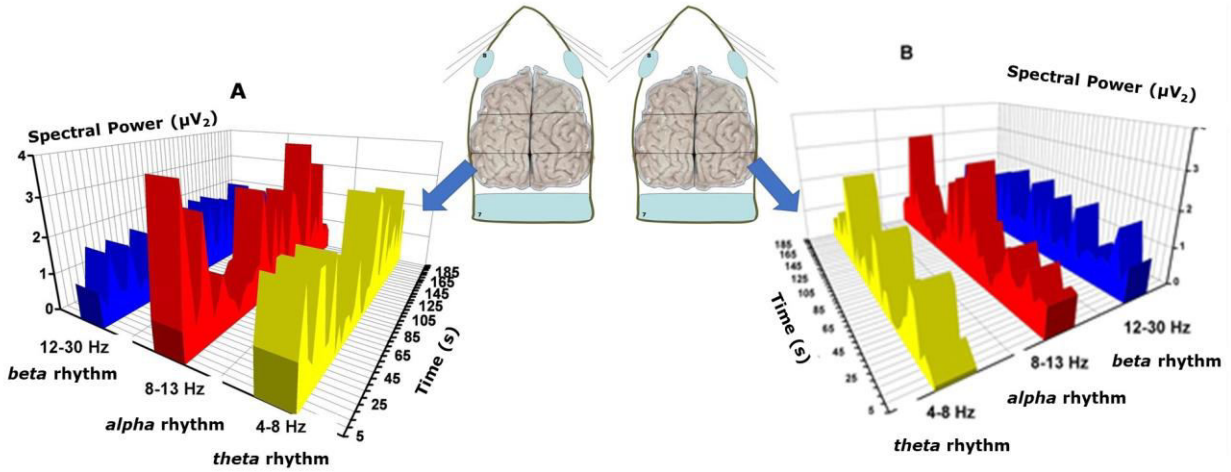


Figure 3.11 *Theta* and *alpha* rhythms spectral power recovery in the central-parietal areas of the left hemisphere to bimodal sensory stimulation (visual, sound)

(A – left hemisphere; B – right hemisphere)

The results of the spectral analysis of the polysomnographic recordings after deprivation of nonREM sleep by applying sound signals leads to an increase in the degree of intra- and interhemispheric asymmetry in the intervals of the *beta* rhythm (15-30 Hz) and *theta* rhythm (4-8 Hz). This means that the changes in spectral power of the *beta* rhythm and *theta* rhythm over time in different derivations from the head surface are not coherent. Interhemispheric asymmetry also manifests itself in quiet wakefulness and drowsiness or superficial sleep (stage I). The most pronounced degree of asymmetry of the order of 7.23-8.1% occurs specifically in the frontal and parietal lobes. Moreover, in the frontal lobes, asymmetry is evident in the *alpha* rhythm range (8-14 Hz). Whereas, in the parietal lobes, oscillations in the theta rhythm range are asymmetric. Predominance of spectral power occurs in the left hemisphere. However, during the sleep period of 3 days of activity in the aquatic environment in the area of the parietal lobes, the occurrence and relative duration, as well as the spectral power of theta rhythm episodes increases from 9% to 22% ($P<0.05$).

The concept of "*Environment promoting functionality*" contains enormous potential not only for Public Health, Prevention and Recovery Programs, but also for the improvement of ecosystems, the rural and urban environment, biodiversity and sustainable development. Environmental factors in combination with vibrations in production and construction, transport affect the functionality of the neuromuscular and musculoskeletal systems. No less important is the application of the methods of restoring the circadian rhythm at the level of regulating the expression of biological clock genes, which will allow the implementation of the "*4P*" algorithm: "*Prediction*", "*Prevention*", "*Personalization*" and "*Participation*". This algorithm includes several subcomponents that have a direct impact on the functioning of vital organs. The neuroprotection and neurorehabilitation program generally provides for the screening of functional status during the sleep-wake cycle, specifically aimed at a comprehensive analysis of restorative sleep after a period of wakefulness and early diagnosis of sleep disorders. It was possible to perform this task in experimental animals, but in humans, under our conditions, it is still technically difficult to implement. It is precisely here that such research is urgently needed: in the early diagnosis of the first manifestations of a syndrome or disorder that is beginning to form. The animal model, which evolutionarily shows a high degree of adaptation to the environmental conditions in which they are forced to use apnea and the ability to sensory monitor their environment during sleep, has great potential. While the syndrome of "*Obstructive Sleep Apnea*" is extremely common in the human population, it reduces work productivity and increases morbidity and mortality. Remarkably, more frequently this syndrome associated with awakening occurs precisely in the phase of paradoxical sleep (REM sleep). REM sleep is often

accompanied by dreams and the experience of violent emotions. The reasons for the formation or exacerbation of obstructive sleep apnea do not lie in the influence of the entire complex of risk factors: noise pollution; dust; night shift work; intense lighting during nighttime transport. Importantly, the EEG theta/beta ratio reflects the relative inability to adapt to such reversals rather than reward sensitivity. Increased spontaneous *theta* activity would reflect a reward state, even in the absence of discrete cues to the magnitude of reward received. The Neuroprotection Program considered that moderate levels of physiological arousal promote workplace performance, while low or too high levels of physiological arousal have been shown to reduce quality and productivity. A neuroprotection and neurorehabilitation program based on methods of strengthening sensorimotor integration ensures the removal and prevention of weakening and impairment of neurological, mental and physical functionality, as well as the acceleration and increase of the efficiency of learning processes.

3.7. Conceptual development of Step 7 of the neuroprotection and neurorehabilitation program, based on the application of biomedical engineering achievements

From the point of view of the natural sciences, the approach to an objective assessment of the mental state should be based on the morphological and functional characteristics of the higher processing centers of the brain. Therefore, the laboratory tests used in the Program should address the global functions of the brain and allow the qualitative and quantitative assessment of the degree of wakefulness and vigilance, concentration and the ability to make correct decisions appropriate to the environmental conditions. Monitoring, prior diagnosis and personalization of neuroprotection programs based on the latest achievements in Biomedical Engineering are a prerequisite for the prevention of neuromuscular and locomotor function disorders and neurodegenerative diseases. With age, according to the data of imaging investigations and the volumetry of brain formations, there is a progression and an increase in the distribution area of atrophic changes in the medial temporal lobe of the cerebral cortex, a significant reduction of the hippocampus and entorhinal cortex, which indicates the initiation and genesis of neurodegenerative transformations of moderate severity, associated with difficulties in navigating the surrounding environment. The ratio between the depth of the frontal horns and the intercaudal distance (CC/IT) reflects the presence of neurodegenerative changes involving the caudal nuclei. A decrease in the ratio between the diameter of the midbrain and the area of the bridge in the representatives of the older age group, compared to the younger ones, proves the progression of neurodegeneration in the area of the midbrain. Against this background, in 3 cases (20%) signs of progressive supranuclear palsy appear. Against the background of signs of atrophic brain changes of varying severity, an increase in the diameters, volume area of the lateral ventricles, the III ventricle and the IV ventricle was revealed.

In the neuroprotection and neurorehabilitation program, there is an urgent need for the screening of adaptation limits, work capacity and degree of fatigue based on the determination of cardiorespiratory fitness (*CRF*), which characterizes psychovegetative interrelations. Detection of early signs of fatigue and overwork is performed to detect functional insufficiency of cardiorespiratory activity. However, these methods are not yet widely used in the occupation model, ie. at the workplace when performing work operations and official activities for the qualitative and quantitative assessment of respiratory and circulatory functionality in real time.

Therefore, measuring technologies and equipment that are harmoniously biologically compatible with the body of an active individual require their development and application not only for diagnosis, but also for regular functional screening during daily work and educational activities. The algorithm for this cardiorespiratory fitness assessment method uses clinical and demographic variables and a combination of heart rate (*HR*) values for the total duration of the functional test time (5 minutes); which shows a fairly high correlation with measured VO_2max values. Field test procedures for cardiorespiratory fitness are proposed to satisfy several criteria,

including validity, longitudinal validity, reliability, safety, and a strong relationship with measures of functionality and adaptability. Based on the technologies for improving human abilities in neuroprotection and neurorehabilitation programs, some physiological methods should be implemented based on the harmonious adaptation of a person to his daily educational and work activities, in general, to his way of life in certain environmental conditions that can be productive and efficient. This program aims to develop and implement a strategy to prevent neurodegenerative disorders of the sensory and neuromotor apparatus, based on the disclosure of the fundamental mechanisms for coordinating its activities according to living conditions; the nature of daily work and service activity; energy productivity; plastic metabolism and nutrition. The practical implementation of the Program includes a combination of complex methods of evaluation and measurement of molecular, cellular, tissue indicators of morphological and functional plasticity, early manifestations of non-degeneration with experimental and occupational modeling of certain types of individual activity. The social and economic importance is the evaluation of a person's abilities to carry out daily vital motor acts and to carry out his professional duties and is, in fact, the initial stage of the program. This evaluation is combined with the determination of the particularities of the diet, the circadian sleep-wake cycle and personal recreation. The program provides that in situations where individual abilities to perform work do not completely coincide with the requirements of a certain type of activity and the time of its completion, fatigue develops faster and more intensely. It is accompanied by the appearance of general fatigue, the functional exhaustion of the body systems most exposed to overload, which leads to a decrease in a person's functional performance, the quality of the final result and work productivity against the background of increased energy losses. For the objective assessment of gait markers and various motor acts performed by individuals, portable motion and vibration sensors are well suited. Such motion sensors, placed in different parts of the body, are often used in Sports, Medicine and Rehabilitation, but can also be used in Occupational Physiology and Occupational Medicine. In particular, the number of steps, step frequency per unit time, and step duration should be determined when quantifying walking efficiency, as well as when analyzing walking speed variability. It is very important to analyze the motor actions when walking, running or performing work operations based on the detection of certain markers that reflect the biomechanical characteristics of the moving parts of the body. Technical approach based on accelerometry allows dosing and strict customization of the functional load to avoid overload. The use of different technical devices for accelerometry demonstrates their potential opportunities in time-synchronized measurements of diurnal activity. The big advantage is that modern vibration sensors and accelerometers use wireless communication and include a microcontroller for custom signal processing and compensation. To increase the flexibility in solving any problems related to monitoring the biomechanical characteristics of daily activity, single and triaxial devices with a built-in temperature sensor are already used.

Therefore, the success of the Program is determined by high technology for the creation of biosensor systems, which use high precision facilities. Namely, progressive manufacturing facilities make possible the nanotechnological creation of modernized biosensor systems with microscopic precision based on the desire to imitate the receptive sensory apparatus of biological objects, including the human body. Biological sensor systems show high sensitivity and selectivity to changes in physical and chemical parameters of different modalities, namely, with engineering biosensor devices with such characteristics. The success of the implementation of neuroprotection and neurorehabilitation programs is determined by the introduction of modern technical innovations in monitoring the architecture of restorative sleep after a period of active wakefulness. The improvement of such monitoring is carried out in the direction of its systematization and integration. The neuroprotection and neurorehabilitation program must include a neurological examination, performed non-invasively and without expensive equipment. For example, the test for the presence of the Babinski reflex is of great diagnostic importance.

Highlighting the manifestations of the formation of coordination deficiencies, muscle weakness and difficulties in muscle control can be performed on the basis of a test for the presence of the Babinski reflex in mature individuals.

Diagnosing early manifestations of neurodegenerative processes and monitoring the effectiveness of the procedures implemented in the program are necessary. The program also requires continuous monitoring of the presence and severity of a block in the conduction of impulses along nerve fibers, i.e. assessment of conductive functionality, especially among individuals practicing intense sports training or complex movements in work activities.

3.8. Conceptual development and testing of Step 8 of the neuroprotection and neurorehabilitation program, which requires the introduction of bioinspiration and biofiltering environmental design technologies

One of the basic components of the Neuroprotection and Neurorehabilitation Program is evolutionarily and physiologically conditioned and consists in the intentional organization of the environment at work and at home, generating a neuromodulatory and neuroprotective effect. Technologies that ensure a neuromodulatory and neuroprotective mechanism are based on the creation of an "*Enriched Environment*" (*EE*). The effects of the "*Enriched Environment*", tested on experimental models in laboratory animals, indicate that sensory-motor enrichment promotes the correction of genetically determined neurological disorders, such as Down syndrome, Alzheimer disease, Huntington disease, Parkinson disease, schizophrenia and autism. Terapeuții ocupaționali au folosit deja cu succes programe de terapie pentru pacienții cu autism și tulburări de procesare a inputului senzorial din mediu ambiant. It has been shown that occupational therapy with the application of the "*Enriched Environment*" model offers improvements in language perception, processing and production and that it develops cognitive skills. During the realization of the Neuroprotection and Neurorehabilitation Program, the "*Enriched Environment*" model is designed with the application of devices and locations that create the opportunity to carry out motor activity; to strengthen the integration of sensory-motor reflex activity; to develop motor skills spontaneously and voluntarily without excessive effort. An experiment using the "*Enriched Environment*" model indicates that an increase in daily activity due to the intensification of behavior motivated by exploration and navigation in space causes the implementation of neuroplasticity mechanisms in the centers of sensory processing and motor coordination. Due to this release of neuroplasticity mechanisms, the "*Enriched Environment*" has a neuroprotective and neurorehabilitative effect, which should be the basis of a program for the targeted prevention of neurodegenerative processes and the repair of damaged elements of the nerve centers. The "*Enriched Environment*" model also provides social incentives, promoting the development of socialization and communication in the community. It is obvious that the development of such skills in people ensures the success of collective work in achieving common goals and solving problems. However, multimodal sensory stimulation must be optimized and avoid overload, as, for example, happens in an urban environment against the background of extremely high population agglomeration, a decrease in the degree of social and environmental safety. Even animal husbandry technologies must apply environmental enrichment to improve the quality of care of captive animals by identifying and providing the necessary environmental stimuli to improve physiological and mental status. Such maintenance and improvement of the animal's physical and mental status is achieved by stimulating a variety of activities by increasing the range and number of locations and objects in the surrounding space that are important for species-specific behavior.

The fundamental testing and confirmation of the neuroprotective neurorehabilitative effect of the environment was carried out using the "*Environmental Enrichment*" (*EE*) experimental model. This model represents one of the most widely used experimental models of eustress in laboratory animals. The application of the "*Enriched Environment*" experimental model showed

the beneficial effects on the processes underlying neuroplasticity and neurorehabilitation. Based on this fact, the concept of environmental enrichment can be applied with full confidence in the workplace, living space, hospitals and rehabilitation centers to induce and facilitate the processes of neurogenesis, increasing the degree of branching of dendrites and axons, strengthening new connections interneurons, the biosynthesis of membrane receptors and ion channels, the formation of vesicles at synaptic contacts, the shift of the balance between anabolism and catabolism towards the predominance of anabolism, etc..

The neuroprotection and neurorehabilitation program is also based on the planning and design of the environment, taking into account the determining importance of adherence to the circadian regime and the role of exogenous zeigebers of the environment, for an efficient and productive recovery, which provides open access to light natural or optimal artificial lighting. Circadian lighting makes a big difference in intensive care units and subsequent recreation and rehabilitation measures. Patients who are admitted to intensive care units are often confused, disoriented, do not know where they are and whether it is day or night. In the Program, biodynamic lighting can be applied, which ensures the simulation of the natural rhythm of day and night, which is very important in periods of increased vulnerability. Biodynamic lighting has a positive effect, especially on the sleep pattern, allowing patients to sleep better at night, and those who sleep better are more relaxed, less confused and recover faster. Natural environmental factors, namely circadian light, also contribute to faster patient rehabilitation.

Conceptual and strategic the neuroprotection and neurorehabilitation program, based on the use of natural environmental factors and individual day-to-day activity, includes practical approaches to social and healing Horticulture. Social and healing horticulture is a methodology of using plants and gardens to improve physical and mental status, as well as communication and thinking skills. It is remarkable that agricultural culture and plant cultivation, as well as animal husbandry, among others, has a history of at least a thousand years and rich traditions in the Republic of Moldova and at the same time represents a significant innovation in modern Occupational Therapy and Rehabilitation. The practical approaches of the Neuroprotection and Neurorehabilitation Program, based on the use of social and healing Horticulture, open wide perspectives in creating an environment that offers effective recreation in an urbanized environment, characterized by the development of archicentralized and overcrowded metropolises, artificially aggressive, harmful to life daily and based on isolation. Gardening allows the creation of a wonderful and flexible environment that conceptually must promote ecosystem restoration processes. Moreover, Social and Healing Horticulture uses the garden as a safe and productive place to develop one's ability to integrate socially. Therefore, such practical approaches are favorable when used as a healing agent for autism. The realization of the Program is based on the design of sets of activities for each individual strictly according to the specific health needs and to work on certain objectives that they want to achieve. The benefits of a sustained and active interest in gardening include: better physical condition through exercise; improving mobility; improved state of mind through a shared sense of purpose and accomplishment; the opportunity to connect with others to reduce feelings of isolation or exclusion from active life; acquiring new skills to improve the chances of finding a job; a better feeling of being in contact with the natural factors of the environment. The implementation of the Neurorehabilitation Program based on Social and Healing Horticulture benefits the human body in several ways: it can be part of a person's rehabilitation process, to help them recover and feel safe after an illness or a difficult moment in life saddle; to recover from a wide range of ailments; to learn new skills; to slow down neurodegenerative processes. The program based on the application of social and healing horticulture also aims at the recovery of individuals after strokes and in the case of cardiovascular insufficiency; those in the early stages of dementia and people with physical and learning disabilities. The Research & Development sector must be actively involved in promoting the benefits of gardening and horticulture activities.

The implementation of the Neuroprotection and Neurorehabilitation Program, based on the design of the environment in medical institutions, is carried out on the main postulates: ensuring security, safety and relaxation; comfort; relative opening. Architectural solutions for interior and exterior design must be improved towards their potential to promote individual and public health. Undeniably, a positive habitual environment must, first of all, contribute essentially to the maintenance of mental and physical health by preventing the impact of stressful environmental factors; the noise; the predominance of artificial light, the diminution of natural circadian light in an isolated environment. The neuroprotection and neurorehabilitation program provides for the provision of free access to light inside the buildings; ventilation and air cleaning; the temperature of the physiological comfort environment, as well as the humidity and air sterility quality are crucial factors in obtaining a positive result. The program for organizing the environment in hospitals, social care homes and nursing homes for the elderly also takes into account the need to arrange workplaces for many employees, because the well-being of the staff greatly influences the quality of treatment and recovery of patients and residents. The concept of "*Healing Architecture*" includes various components and functions oriented towards hygiene, accessibility and touch-free operation of windows and doors. "Healing architecture" also includes the following elements: prevention of environmental distress; the noise caused by the slamming of doors; crossing barriers etc. Tests with the application of imitation of the "Enriched Environment" and favorable adaptive environmental conditions showed psychomotor facial reactions, proving the maintenance of a positive emotional state. Modern educational institutions, industries and departments must really follow an inclusive policy of socializing people with health problems.

The obtained results indicate that, indeed, the presentation of a positive sensory signal from the environment is associated with a significant decrease in the displacement of the points in the *m. corrugator supercilii* region (by 13.8%, P<0.05). This decrease is manifested against the background of an increase in the degree of displacement in the area of the *zygomaticus muscles* by 37.6% (P<0.05) (Fig. 3.12, left).

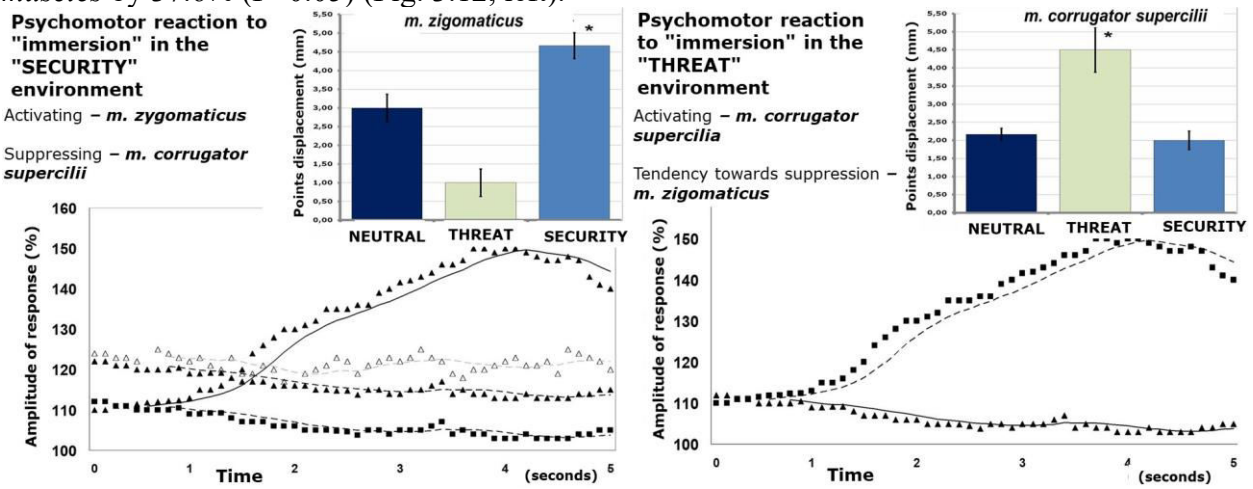


Figure 3.12 Psychomotor reactions evaluated using FACS (Facial Action Coding System) when simulating a non-threatening environment ("Security"): – *m. zigomaticus*; – *m. buccinator*; – *m. orbicularis*; – *m. corrugator* **and an aggressive environment ("Threat"):** – *m. corrugator supercilii*; – *m. zigomaticus*

The presentation of a sensory signal, which informs about a threat, the localization zone of the undulating *corrugator supercilii muscles* causes a displacement of the eyebrows and the ridges of the eyebrows and moves statistically significantly by 17.6% (P<0.05), as well as the

localization zone of the *orbicularis oculi muscles* by 19.7% ($P<0.05$), manifested as expansion and contraction of the eye sockets. Comparisons were made with the estimation results in the case of applying a sensory stimulus from the neutral environment in the sense of security/threat.

We assume that the methodology of identifying and capturing facial and body movements by applying the Facial Action Coding System (FACS) can be successfully used for the qualitative and quantitative analysis of sensory-motor integration during verbal and non-verbal communication. Data from the analysis of psychomotor reactions in response to sensory flow modeling objectively reflect the degree of sensory-motor integration and the nature of the individual's reactivity to a complex of communicative signals.

Moreover, motion capture and optical tracking technologies can be successfully used to objectively recognize manifestations of aggression, which significantly affect the characteristics of verbal and nonverbal communication. In response to the imitation of a threatening environment, the manifestation of facial movements in the muscle area: *corrugator supercilii* and *orbicularis oculi*, is significantly increased (Fig. 3.12, right). In addition, a significant 23.5% ($P<0.05$) shift of points in the coordinate system was detected in the area of localization of the *nasal muscles* and *levator labii superioris*, manifested as a wrinkling of the nose, indicating disgust.

For the successful implementation of neuroprotection programs based on the action of environmental factors, daily activity and nutrition, there is an urgent need for design and readaptation of Educational Technologies.

In educational technologies, innovations are needed that ensure the formation of a favorable, promoting and motivating environment for learning processes, formation of new educational and work skills, adaptation to modern society and, in particular, to the collective and the work team. At the forefront of innovations is the mandatory involvement of students of different training levels in the implementation of projects, which aim to expand the limits of adaptation and neuroprotection of a modern person in the dynamics of work, service activity and daily recreation.

GENERAL CONCLUSIONS AND RECOMMENDATIONS

1. The measures provided by stage 1 of the neuroprotection and neurorehabilitation program, aimed at stimulating the functionality and adaptability of the gas exchange system in interaction with the circulatory system, in particular cerebral blood flow, ensure the increase of aerobic fitness, tolerance to hypoxia, biosynthetic productivity of factors neurotrophic, the neuromodulatory effect of monoaminergic systems.
2. Combining aerobic and anaerobic training with diets with a low glycemic index and enriched with proteins in combination with preparations of plant origin with adaptogenic action ensures the balancing of energy and plastic metabolism, changing the ratio between adipose and muscle tissues towards the predominance of skeletal muscle tissue.
3. The specific characteristics of daily activity at the workplace, as shown by the experimental model "*Night shift work*" and occupational models with exposure to multisensory and motor efforts during periods of sleep (recreation) and wakefulness (preoccupation), modify the architecture sleep, disrupting the cyclicity of subsequent restorative sleep, increasing the incompleteness of nonREM sleep and REM sleep, and reducing *delta*, *alpha*, and *theta* rhythms in association with asymmetry.
4. The neuroprotective, restorative and healing effects of plant-derived adaptogens are produced in combination with aerobic, anaerobic training and optimized nutrition, increasing aerobic fitness, adaptability and balancing heart rate variability and body composition towards a predominantly skeletal muscle proportion.

5. The individually selected proprioceptive training complex within the kinetotherapeutic programs ensures the development and consolidation of the plastic transformations of the nerve, muscle, articular and ligamentous tissues, the development of professional skills and the implementation of the neurorehabilitation program.
6. The types of professional activities associated with the formation of an overload on the sensory systems of various modalities (visual, sound), the action of local and general vibrations, the increase of the electromagnetic background, cause a decrease in the neuroprotective properties of the nerve centers, increasing the risk of the pathogenesis of tissue degeneration, neurodegeneration, insufficiency of monoaminergic systems, neurotrophins and the development of Alheimer and Parkinson diseases.
7. The enriched environment model demonstrates the importance for the brain centers of the novelty of the environment factors, their safety and hedonic nature, the promotion of a variety of developmentally appropriate daily activities and the stimulation of central reward systems.

Practical recommendations

1. In order to look for new opportunities to prevent the development of suffering and occupational diseases, it is necessary, first of all, to learn how to objectively determine adaptive limits and identify early signs of the manifestation of maladaptive morphofunctional transformations in sensory-control centers engine in the dynamics of work activity in a stressful environment.
2. The projecting and modern construction of rural and urban environments, as well as the organization of workplaces should be justified from an evolutionary, ecological and physiological point of view in order to conserve, restore ecosystems, ensure sustainable development and biodiversity, food and social security.
3. The system of professional education, development of the skills of the workforce should be built in accordance with the achievements of modern neurosciences, which prove the urgent need for a motivating, satisfying environment that promotes a variety of activities and ensures the implementation of mechanisms of neuroplasticity and neuroprotection.
4. The transformation of the urban and rural environment should ensure the creation of a barrier-free environment, harmony with the surrounding landscape, exposure to natural environmental factors and prevention of isolation in an artificial environment.

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LIST OF THE AUTHOR'S PUBLICATIONS ON THE THESIS TOPIC

1. **Specialty books**

1.1. single-author specialty books

1. **БАЧУ, А.Я.** *Пластичность нервных центров и сенсорно-моторное управление*. Tiraspol: Editura Universității din Transnistria; 2020. 280 p.

1.2. collective specialty books (with specification of personal contribution)

2. MEREUTA, I., **BACIU, A.,** LISTOPADOVA, L. FEDAS, V., CARAUS, V., SIRBU, E. *Mediul ambiant – factor primordial al sănătății globale*. Chișinău: Poliviz-Design SRL, 2023: 180 p. (Personal contribution – 40%)
3. MEREUȚĂ, I., **BACIU, A.,** FEDAȘ, V., LISTOPADOVA, L. *Mediul şi activitatea zilnică în extinderea neuroplasticității.* Chișinău: Poliviz-Design SRL. 2023. 256 p. (Personal contribution – 40%)
4. MEREUȚĂ, I., **BACIU, A.,** FEDAȘ, V. *Fortificarea sănătății: plasticitatea şi diminuarea riscurilor metabolice.* Chișinău: Tipografia „Poliviz-Design”, 2022, 206 p. ISBN 978-9975-3434-8-0. (Personal contribution: 40%)

2. Articles in scientific journals

2.1. in journals from the Web of Science and SCOPUS databases

5. **BACIU, A. Ja.,** FEDAS, V.V., MEREUTA, I.E., CECAN, M., LISTOPADOVA, L.A. Biomedical engineering and occupational therapy approach in technologies for enhancement human labor and defense abilities. In: Proceedings of ICNBME-2021 (November 3-5, 2021, Chisinau, Moldova). Cham, Switzerland: Springer, Vol. 87, 2021, p. 715-720, Doi: 10.1007/978-3-030-92328-0_90. ISBN: 978-3-030-92328-0.
6. LISTOPADOVA, L., **BACIU, A.,** MEREUTA, I., IONESCU-TIRGOVISTE, C., CARNICIU, S., FEDAS, V. Prevention of eating behavior disorders by indirect balancing of activating and reward systems. In: *Proceedings of The Romanian Academy. Series B: Chemistry, Life Sciences and Geosciences.* 2020, 22(2), p. 105-109. ISSN: 1454-8257. (database: www.webofknowledge.com) (disponibil: https://acad.ro/sectii2002/proceedingsChemistry/doc2020-2/Art09.pdf)

2.3. in journals from the National Register of professional journals (indicating the category)

7. LISTOPADOVA, L., **BACIU, A.**, ŞEPTIŢCHI, V.. Influenţa stimulării electrice a sistemului orexinergic activator al hipotalamusului asupra comportamentului alimentar la şobolanii albi. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţele vieţii*. 2017, nr. 1(331), pp. 32-38. (Cat. B) ISSN 1857-064X. (electronic deposit: https://ibn.idsi.md) (available: https://ibn.idsi.md/sites/default/files/imag_file/007_Listopadova%20Liudmila%2C%20Baciu%20Anatolie%2C%20%C5%9Eepti%C5%A3chi%20Vladimir.pdf)
8. LISTOPADOVA, L., SHEPTITSKY, V., MEREUŢĂ, I., **BACIU, A.** Environmental factors, circadian activity, eating behavior as a means of preventing respiratory syndromes. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţele vieţii*, 2022, nr. 3(347), pp. 25-31. ISSN 1857-064X. DOI: 10.52388/1857-064X.2022.3.02 (Cat. B). (electronic deposit: https://ibn.idsi.md) (available: https://ibn.idsi.md/sites/default/files/imag_file/25-31_36.pdf)
9. **BACIU, A.,** LISTOPADOVA, L., FEDAŞ, V. Combination of somatosensory stimulation and diet with a reduced glycemic index in preventing and correcting of obesity. *In: Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţele vieţii.* 2021, nr. 1(343), pp. 31-37. doi: org/10.52388/1857-064X.2021.1.04. ISSN 1857-064X. (Cat. B) (electronic deposit: https://ibn.idsi.md) (available: https://ibn.idsi.md/sites/default/files/imag_file/31-37_26.pdf)
10. ЛИСТОПАДОВА, Л., **БАЧУ, А.**, ШЕПТИЦКИЙ, В., ФИЛИПЕНКО, Е. Особенности экспрессии саногенных эмоций у белых крыс при реализации пищевого поведения. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţele vieţii*, 2021, nr. 2(344), pp. 82-91. ISSN 1857-064X. DOI: 10.52388/1857-064X.2021.2.06 (Cat. B). (electronic deposit: https://ibn.idsi.md) (available: https://ibn.idsi.md/sites/default/files/imag_file/82-91_10.pdf)
11. **BACIU, A.** Riscuri majore ale efectelor carcinogene nocive de mediu ambiant în întreprinderile din industria uşoară. În: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale*. 2024, nr. 1(78), 2024, pp. 256-263. ISSN 1857-0011. (Cat. B). (electronic deposit: https://ibn.idsi.md)
12. **BACIU, A.** Balancing sensory stimulation/deprivation from the environment in health-forming technologies. În: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale*. 2024, nr. 1(78), 2024, pp. 264-267. ISSN 1857-0011. (Cat. B). (electronic deposit: https://ibn.idsi.md)

2.4 in other recognized journals

13. **БАЧУ, А.Я.**, ЛИСТОПАДОВА, Л.А. Нейромодуляторное действие двигательной активности в цикле бодрствование-сон. В: *Вестник Приднестровского Университета. Серия: Медико-биологические и химические науки.* 2022, 2(71), с. 56-62. E-ISSN 1857-4246. (electronic deposit: https://elibrary.ru) (available: https://elibrary.ru/download/elibrary_49610666_31513650.pdf)
14. ЛИСТОПАДОВА, Л.А., **БАЧУ, А.Я.** Взаимодействие центров латеральной области и супрахиазматического ядра гипоталамуса в механизмах регуляции циркадианного биоритма. В: *Вестник Приднестровского университета. Серия: Медико-биологические и химические науки*. 2023, 2(74), с. 16-22. (electronic deposit: http://spsu.ru) (available: http://spsu.ru/images/files/science/Vestnik_2_2023.pdf)
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forming-technologies-based-on-the-balancing-sensory-stimulation-deprivation-from-the-environment.pdf)

3. Articles in conference proceedings and other scientific events

3.2. in the works of scientific events included in other databases accepted by ANACEC

16. **BACIU, A. Ja.**, MEREUTA, I., FEDASH, V., LISTOPADOVA, L. Arousal from sleep, alertness induced by bimodal signals during „environment-person" communication. In: *Proceeding of The 12th International Conference on Electronics, Communications and Computing „IC ECCO-2022"*. Chisinau, Republic of Moldova, 2022 p. 50-54. (database: www.ibn.idsi.md) (depozit electronic: https://repository.usmf.md;) (available: http://repository.utm.md/bitstream/handle/5014/21826/Int-conf-ECCO-2022-p50-54.pdf?sequence=1&isAllowed=y)
17. **BACIU, A. Ja.,** FEDAS, V.V., MEREUTA, I.E., CECAN, M., LISTOPADOVA, L.A. Biomedical engineering and occupational therapy approach in technologies for enhancement human labor and defense abilities. In: Proceedings of ICNBME-2021 (November 3-5, 2021, Chisinau, Moldova). Cham, Switzerland: Springer, Vol. 87, 2021, p. 715-720, Doi: 10.1007/978-3-030-92328-0_90. ISBN: 978-3-030-92328-0. (electronic deposit: https://ibn.idsi.md) (baza de date: http://link.springer.com) (available: https://link.springer.com/chapter/10.1007/978-3-030-92328-0_90)

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18. **БАЧУ, А.,** МАНТОПТИН, А. Адаптивные и дезадаптивные нейропластические преобразования в центрах нервного регулирования сенсорно-моторной интеграции и ориентации в водной среде. În: Culegerea de lucrări științifice ale Conferinței științifice naționale consacrate jubileului de 90 de ani din ziua nașterii acad. Boris Melnic. Chișinău: CEP USM, 2018, p. 56-59. ISBN 978-9975-71-971-1. (electronic deposit: https://ibn.idsi.md)
19. **BACIU, A.,** FURDUI, V., LEORDA, A., LISTOPADOVA, L. The evaluation of the sano-/dissanogenity of the person-environment communication by means of the immersion in multi-sensory surrounding medium. În: Culegerea de lucrări ale Conferinței științifice naționale cu participare internațională „*Integrare prin cercetare și inovare*", 8-9 noiembrie 2018. Chișinău: CEP USM, 2018, p. 53-57. ISBN 978-9975-142-49-6. (electronic deposit: https://ibn.idsi.md)
20. LEORDA, A., FURDUI, V., **BACIU, A.,** PODARU, A. Utilizarea componentei verbale pentru psihocorectie in functie de tipul de temperament. În: Culegerea de lucrări ale Conferinței științifice naționale cu participare internațională „*Integrare prin cercetare și inovare*", 8-9 noiembrie 2018. Chișinău: CEP USM, 2018, p. 79-82. ISBN 978-9975-142-49-6. (electronic deposit: https://ibn.idsi.md)
21. **BACIU, A.,** FURDUI, V., LEORDA, A., LISTOPADOVA, L. Vulnerabilitatea interrelaţiilor psihosomatice, psihovegetative în dependenţă de statutul funcţional al sistemelor respirator şi locomotor în perioada de vârstă 22-45 ani. În: Culegerea de lucrări ale Conferinței științifice naționale cu participare internațională „*Integrare prin cercetare și inovare*", 7-8 noiembrie 2019. Chișinău: CEP USM, 2019, p. 58-62. ISBN 978-9975-149-46-4. (electronic deposit: https://ibn.idsi.md)
22. FURDUI, V., **BACIU, A.,** LEORDA, A., POLEACOVA, L., CIOCHINĂ, M. Expresia mimică a emoţiilor ca indicator al interrelaţiilor psihosomatice sanogene şi dissanogene. În: Materialele Conferinței Științifice Internaționale „*Sănătatea, medicina și bioetica în societatea contemporană: studii inter și pluridisciplinare*", 29-30 octombrie 2021, ediția a IV-a. Chișinău: Print Caro, 2021, p. 324-332. ISBN 978-9975-56-935-4. (electronic deposit: https://ibn.idsi.md)
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25. **BACIU, A.**, LISTOPADOVA, L. Achieving a maximum program for creating and maintaining the human workforce by optimizing the circadian sleep-wake and fasting-eating cycles. În: Materialele Conferinței Științifice Internaționale „*Sănătatea, medicina și bioetica în societatea contemporană: studii inter și pluridisciplinare*”, 6-7 octombrie 2023, ediția a VI-a. Chișinău: Print Caro, 2023, p. 303-309. ISBN 978-9975-82-334-0. (electronic deposit: https://repository.usmf.md; www.ibn.idsi.md) (available: https://conferinte.stiu.md/sites/default/files/evenimente/S%C4%83n%C4%83tatea%2C%20medicina%20%C8%99i%20bioetica%20%C3%AEn%20societatea%20contemporan%C4%83%2C%20Conf.%202023.pdf)
26. FEDAȘ, V., MEREUȚĂ, I., **BACIU, A.**, OJOVAN, V., LISTOPADOVA, L., POLEACOVA, L. Stresul oxidativ și rolul său în declanșarea și evoluția inflamației și sindromului metabolic. În: Materialele Conferinței Științifice Internaționale „*Sănătatea, medicina și bioetica în societatea contemporană: studii inter și pluridisciplinare*”, 6-7 octombrie 2023, ediția a VI-a. Chișinău: Print Caro, 2023, p. 296-302. ISBN 978-9975-82-334-0. (depozit electronic: https://repository.usmf.md; www.ibn.idsi.md) (available: https://conferinte.stiu.md/sites/default/files/evenimente/S%C4%83n%C4%83tatea%2C%20medicina%20%C8%99i%20bioetica%20%C3%AEn%20societatea%20contemporan%C4%83%2C%20Conf.%202023.pdf)
27. MEREUȚĂ, I., FEDAȘ, V., POLEACOVA, L., **BACIU, A.**, CARAUȘ, V., NĂSTASE, C. Diabetul zaharat tip 2 – o componentă de bază a sindromului metabolic și locul său în structura morbidității populaționale generale. În: Materialele Conferinței Științifice Internaționale „*Sănătatea, medicina și bioetica în societatea contemporană: studii inter și pluridisciplinare*”, 6-7 octombrie 2023, ediția a VI-a. Chișinău: Print Caro, 2023, p. 290-296. ISBN 978-9975-82-334-0. (electronic deposit: https://repository.usmf.md; www.ibn.idsi.md) (available: https://conferinte.stiu.md/sites/default/files/evenimente/S%C4%83n%C4%83tatea%2C%20medicina%20%C8%99i%20bioetica%20%C3%AEn%20societatea%20contemporan%C4%83%2C%20Conf.%202023.pdf)
28. **BACIU, A.**, LISTOPADOVA, L. Interdisciplinary interaction in the research and development of a human living environment that heals rather than kills. În: Materialele Conferinței științifice naționale cu participare internațională dedicată Zilei Internaționale a Științei pentru Pace și Dezvoltare „*Integrare prin Cercetare și Inovare*”, 9-10 noiembrie 2023. Științe ale naturii și exacte, Chișinău, 2024, p. 38-43. ISBN 978-9975-62-687-3. (electronic deposit: www.ibn.idsi.md) (available: https://cercetare.usm.md/wp-content/uploads/Culegerea_de_articole_Seria_Stiinte_ale_naturii_si_exacte.pdf)

4. Patents and other intellectual property objects (OPI)

4.2. issued by the State Agency for Intellectual Property

29. **BACIU, A.,** MEREUȚĂ, I., CARAUȘ, V., FEDAȘ, V. *Supliment alimentar biologic activ cu activitate antioxidantă și adaptogenă*. Brevet de invenție de scurtă durată 1655 MD. Nr. depozit: s20220019, data depozit: 2022.03.18. BOPI, 12, 2022, p. 65-66. ISSN 2345-1815.
30. MEREUȚĂ, I., FEDAȘ, V., CARAUȘ, V., **BACIU, A.** *Compoziție fitoterapeutică pentru obținerea infuziei apoase cu efect de reducere a masei corporale*. Brevet de invenție de scurtă durată 1498 MD. Nr. depozit: s20200104, data depozit: 2020.08.26. BOPI, 2, 2021, p. 47-48. ISSN 2345-1815.
31. CARAUȘ, V, MEREUȚĂ, I., FEDAȘ, V., **BACIU, A.** *Compoziție fitoterapeutică pentru obținerea infuziei apoase cu efect de reducere a lipoproteidelor de densitate joasă*. Brevet de invenție de scurtă durată 1499 MD. Nr. depozit: s20200105, data depozit: 2020.08.26. BOPI, 2, 2021, p. 48. ISSN 2345-1815.
32. FEDAȘ, V., MEREUȚĂ, I., CARAUȘ, V., **BACIU, A.** *Compoziție fitoterapeutică pentru obținerea infuziei apoase cu efect antihipertesiv*. Brevet de invenție de scurtă durată 1500 MD. Nr. depozit: s20200106, data depozit: 2020.08.26. BOPI, 2, 2021, p. 48-49. ISSN 2345-1815.

5. Other works and achievements specific to different scientific fields

5.1. Theses in journals from the Web of Science and SCOPUS databases

33. **BACIU, A.**, FEDAŞ, V., CARNICIU, S. Promoting of hypoxia tolerance of the motor respiratory centre and sensorimotor cortex during repetitive underwater diving by the adaptation to hypobaric hypoxia. In: *Romanian Medical Journal*. Vol. LXVI. Suppl. Al XIII-lea Congres anual al Asociației Medicale Române. 2019. p. 23-24. (database: www.scopus.com) (available: https://rmj.com.ro/articles/2019.s/RMJ_2019_S.pdf)
34. CARNICIU, S., **BACIU, A.**, FEDAŞ, V. The attenuation of energy metabolic misbalance by means of aerobic, hypoxic, hypothermal adaptation and environmental optimization at recreation resort center. In: *Balneo Research Journal*. 2019, 10(3), p. 430. ISSN: 2069-7597, eISSN: 2069-7619. (database: www.webofknowledge.com) (available: https://bioclima.ro/Balneo276.pdf)
35. **BACIU, A.,** FEDAŞ, V., MEREUȚĂ, I., IONESCU-TÎRGOVIȘTE, C., CARNICIU, S. The revival of the traditions of health creative tourism in the Dniester-Prut-Danube region. In: *Balneo Research Journal*. 2020, 11(3), P10. ISSN: 2069-7597, eISSN: 2069-7619. (database: www.webofknowledge.com) (available: https://ibn.idsi.md/sites/default/files/imag_file/p-P10.pdf)
36. **BACIU, A.**, FEDAS, V., MEREUTA, I., IONESCU-TÎRGOVIȘTE, C., CARNICIU, S. Prevention of disability by early and timely diagnosis of neurodegeneration using biomedical engineering method. In: *Balneo and PRM Research Journal*. 2021, Vol.12, No.3: p. L22 (database: www.webofknowledge.com) (available: https://bioclima.ro/Balneo452.pdf)
37. **BACIU, A.,** FEDAS, V., MEREUTA, I., IONESCU-TÎRGOVIȘTE, C., CARNICIU, S. LISTOPADOVA, L. Environmental and lifestyle factors in neuromodulation of central monoaminergic neurotransmitter systems. In: *Balneo and PRM Research Journa*l (Congress Abstracts, National Congress of Physical and Rehabilitation Medicine & Balneology with International participation. Slănic Moldova, 3-7 September, Techirghiol, 7-10 September). 2022, Vol.13, No 3, L02. e ISSN 2734-8458. p ISSN 2734-844X. (electronic deposit: http://www.webofknowledge.com/; https://mjl.clarivate.com/home; https://ibn.idsi.md/) (available: http://bioclima.ro/Balneo510.pdf)
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40. **BACIU, A.,** MEREUTA, I., FEDAS, V. Psychosomatic and psychovegetative vulnerability in dependence on gas exchange function in aged sport veterans and non-trained individuals. *Sănătate Publică, Economie și Management în Medicină* (*I-ul Congres Național de Geriatrie și Gerontologie din Republica Moldova, cu participare internațională*, 23-24 septembrie 2021), 2021, Supliment la nr. 3(90), 39-40. ISSN 1729-8687. E-ISSN 2587-3873. (Cat. B)
41. FEDAS, V., MEREUTA, I., POLEACOVA, L., LISTOPADOVA, L, **BACIU, A.** The balance of metabolic supply of adipose, bone and muscle tissues plasticity in aged sport veterans. *Sănătate Publică, Economie și Management în Medicină* (*I-ul Congres Național de Geriatrie și Gerontologie din Republica Moldova, cu participare internațională*, 23-24 septembrie 2021), 2021, Supliment la nr. 3(90), 40-41. ISSN 1729-8687. E-ISSN 2587-3873. (Cat. B)

5.3. Theses in the works of scientific events included in other databases accepted by ANACEC

42. CIOCHINĂ V.C., FURDUI V.T., LEORDA A.I., **BACIU A.J.,** JITARI YU.N., BOTNARU N.D. The role of communication in the formation and manifestation of mental health. B: *Proceedings of the XV International interdisciplinary Congress „Neuroscience for Medicine and Psychology*", Sudak, Crimea, May 30-June 10, 2019, p. 459. e-ISBN 978-5-317-06140-1. print-ISBN 978-5-317-

06141-8. (database: https://ibn.idsi.md/) (available: http://brainres.ru/work/Sudak%202019_15%20Congress%20Proceeding_electron%20version.pdf)

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44. **BACIU, A.** Atenuarea dezechilibrului metabolic şi îmbunătăţirea stării psihoemoţionale prin aplicarea programului de exerciţii fizice. In: *Life sciences in the dialogue of generations: Connections between universities, academia and business community*: *Proceedings of the National Conference with International Participation*, October 21-22, 2019. Chişinău, 2019, p. 81-82. ISBN 978-9975-108-83-6. (electronic deposit: https://ibn.idsi.md/) (available: https://ibn.idsi.md/sites/default/files/imag_file/Abstract_book_Conferinta_USDC_2019.pdf)
45. **BACIU, A.Ja.,** FEDAS, V.V., MEREUTA, I.E., CECAN, M., LISTOPADOVA, L.A. Biomedical engineering and occupational therapy approach in technologies for enhancement human labor and defense abilities. *The 5th International Conference on Nanotechnologies and Biomedical Engineering*: Abstract Book. November 3-5, 2021, Chisinau, p. 124. ISBN 978-9975-72-592-7. (database: https://ibn.idsi.md/) (available: https://ibn.idsi.md/vizualizare_articol/142670)
46. TÎBÎRNĂ, G., MEREUŢĂ, I., **BACIU, A.**, FEDAŞ, V. Beneficiile economice ale utilizării erbicidelor asociate cu impactul neurodegenerativ şi cancerogen. *Ecological and Environmental Chemistry-2022: Abstract of the 7th International Conference*, March 3-4, 2022, Chisinau, Republic of Moldova, Ediția 7, 2022, Vol. 2, p. 23. (depozit electronic: http://eec-2022.mrda.md; https://ibn.idsi.md) (available: http://eec-2022.mrda.md/wp-content/uploads/2016/02/EEC-2022-Abstract-Book-Vol-2-Final.pdf)
47. **BACIU, A. JA.**, MEREUTA, I., LISTOPADOVA, L., FEDASH, V. Environmental, activity-dependent modulation of theta rhythm during rem sleep by its selective deprivation and subsequent rebound. In: *Proceeding of The 5th International Conference on Nanotechnologies and Biomedical Engineering „ICNBME-2023"*. 20-23 September, Chisinau, Republic of Moldova, 2023 p. 114. (electronic deposit: https://ibn.idsi.md) (available: https://ibn.idsi.md/sites/default/files/imag_file/114_1_0.pdf)

5.4. Theses in the works of scientific manifestations included in *Register of materials published on the basis of scientific events organized in the Republic of Moldova*

48. FEDAȘ, V., TIMOȘCO, M., MEREUȚĂ, I. BOGDAN, V., NĂSTASE, C., **BACIU, A.** Factorii declanșatori ai unor patologii metabolice. În: Materialele Conferinței Științifice Internaționale „*Sănătatea, medicina și bioetica în societatea contemporană: studii inter și pluridisciplinare*", 29-30 octombrie 2021, ediția a IV-a. Chișinău: Print Caro, 2021, p. 310-311. ISBN 978-9975-56-935-4. (electronic deposit: https://ibn.idsi.md/)
49. LISTOPADOVA, L., **BACIU, A.,** MEREUȚĂ, I., POLEACOVA, L., OJOVAN, V., NĂSTASE, C., FEDAȘ, V. Prevenirea tulburărilor comportamentului alimentar prin echilibrarea activității a sistemelor de activare și de recompensare. În: Materialele Conferinței Științifice Internaționale „*Sănătatea, medicina și bioetica în societatea contemporană: studii inter și pluridisciplinare*", 29-30 octombrie 2021, ediția a IV-a. Chișinău: Print Caro, 2021, p. 347-349. ISBN 978-9975-56-935-4. (electronic deposit: https://ibn.idsi.md/)
50. **BACIU, A.,** MEREUȚĂ, I., IONESCU-TÎRGOVIȘTE, C., POLEACOVA, L., FEDAȘ, V. Strategia de dezvoltare a populației a sănătății individuale în medicina viitorului apropiat. În: Materialele Conferinței Științifice Internaționale „*Sănătatea, medicina și bioetica în societatea contemporană: studii inter și pluridisciplinare*", 29-30 octombrie 2021, ediția a IV-a. Chișinău: Print Caro, 2021, p. 361-363. ISBN 978-9975-56-935-4. (electronic deposit: https://ibn.idsi.md/)
51. **BACIU, A.,** LISTOPADOVA, L., FEDAS, V. The necessity for modernization of the adaptogenic concept on the basis of combining the application of adaptogens with the optimization of the lifestyle. În: Culegerea de lucrări ale Conferinței științifice naționale cu participare internațională dedicată aniversării a 75-a a Universității de Stat din Moldova „*Integrare prin cercetare și inovare*".

Chișinău: CEP USM, 2021, p. 18-20. ISBN 978-9975-152-48-8. ISBN 978-9975-158-60-2. (electronic deposit: https://ibn.idsi.md/)

52. MEREUȚĂ, I., TOMȘA, A., **BACIU, A.,** CEBOTARI, A., FEDAȘ, V. Boala coronavirus și factorii cu risc metabolic crescut – probleme și soluții. In: *Biotehnologii moderne – soluții pentru provocările lumii contemporane*: Lucrările Simpozionului științific național cu participare internațională, 20-21 mai, 2021, Chișinău, p. 71. ISBN 978-9975-3498-7-1 (electronic deposit: https://ibn.idsi.md/) (available: https://doi.org/10.52757/imb21.037)
53. **BACIU, A.**, MEREUȚĂ, I., FEDASH, V. Preventing the detrimental effects of intermittent asphyxia during rem sleep by improving adaptability. In: *Life sciences in the dialogue of generations: Connections between universities, academia and business community:* Abstract book of The National Conference with International Participation. 14-15 September, 2023, Chisinau, Republic of Moldova, p. 110. ISBN 978-9975-3430-9-1. (electronic deposit: www.ibn.idsi.md) (http://agarm.md/wp-content/uploads/2023/09/ABSTRACT-BOOK_2023.pdf)
54. **BACIU, A. Ja.**, MEREUTA, I., FEDAS, V., LISTOPADOVA, L. Prophylaxis of respiratory syndromes by neuroimmunomodulatory action of natural environmental factors. In: *Life sciences in the dialogue of generations: Connections between universities, academia and business community:* Abstract book of The National Conference with International Participation. 29-30 September, 2022, Chisinau, Republic of Moldova, p. 123. (electronic deposit: https://igfpp.md/evenimente; www.ibn.idsi.md) (available: http://agarm.md/wp-content/uploads/2022/10/Culegerea_22.09.pdf)

5.5. Teze în reviste recunoscute

55. **БАЧУ, А.Я.** Действие гипоксии и гиперкапнии, вызванных экспериментальным погружением в подводном колоколе, на биоэлектрическую активность головного мозга. В: *International Scientific Investigations Journal* (Сборник статей ЦНС "Международные научные исследования" по материалам VII международной научно-практической конференции: «Проблемы и перспективы современной науки», Часть 2, Вып. №7, 25 мая 2016). 2016, сс. 133-138. ISSN 4684-1407.
56. **БАЧУ. А.Я.** Показатели электрогастроэнтерограммы как индикатор адапто- и стрессогенности анаэробного силового тренинга. В: *Вестник приднестровского университета. Серия: Медико-биологические и химические науки*. 2019, № 2 (62), сс. 88-95. E-ISSN 1857-4246.
57. **БАЧУ. А.Я.** Применение индивидуальной программы адаптации на основе аэробного тренинга для нормализации энергетического метаболизма и состава тела. В: *Вестник приднестровского университета. Серия: Медико-биологические и химические науки.* 2019, № 2 (62), сс. 82-88. E-ISSN 1857-4246.
58. **БАЧУ, А.Я.**, Роскошанская Л.А., Былич Л.Г, Пержу Е.С. Проявление нейродегенеративных процессов в головном мозгу человека в зависимости от образа жизни, пола и возраста. В: *Вестник приднестровского университета. Серия: Медико-биологические и химические науки*. 2018, 2(59), сс. 30-36. ISSN 1857-1166.
59. **БАЧУ, А.Я.**, ЛИСТОПАДОВА, Л.А. Трудо- и обороноспособное общество – достояние Республики, формируемое здоровьеобразующими технологиями. В: *Вестник приднестровского университета. Серия: Медико-биологические и химические науки.* 2021, 2(68), сс. 70-76. eISSN: 1857-4246.

ADNOTARE

Baciu Anatolie "Program de neuroprotecţie şi neuroreabilitare bazat pe acţiunea multimodală combinată a factorilor de mediu, activitate zilnică individuală şi alimentaţie ecologică". Teză de Doctor habilitat în Ştiinţe Biologice, Chişinău, 2024.

Structura tezei: introducere, trei capitole, concluzii generale şi recomandări practice, bibliografie din 497 de titluri, 5 anexe, 234 pagini de text de bază, 89 figuri, 9 tabele. Rezultatele obţinute sunt publicate în 67 de lucrări ştiinţifice.

Cuvinte cheie: factorii de mediu ambiant, remodelare adaptivă, neuroplasticitate, integrare senzorial-motorie, ciclul somn-veghe, funcționalitate neuromusculară, compoziție corporală

Scopul lucrării: Dezvoltarea unei baze științifice fundamentale, testarea în experiment și aplicarea în screening-ul stării de sănătate a persoanelor cu activități profesionale în anumite condiţii ai mediului şi unei abordări tehnologice bazate pe exerciții senzoriale-motorii în condiții optimizate pentru a preveni bolile neurodegenerative (Alzheimer, Parkinson)

Obiectivele lucrării: evidențierea mecanismelor de bază ale acţiunii neuroprotectoare şi neuroreabilitative ale combinaţiei factorilor multimodali de mediu, promovării funcţionalităţii și adaptabilității sistemului senzorial-motor integral pentru optimizare și echilibrare schimbului de gaze și circulaţiei sanguine; aplicarea unui set de metode de modelare experimentală și studiere a modelului de personalitate-mediu-ocupație-performanță; testarea fundamentală a acțiunii neuromodulatoare și neuroprotectoare a sistemelor monoaminergice ale creierului, declanșate și menținute de factorii de mediu (hipoxiei cu hipercapnie), activitatea zilnică, ciclul somn-veghe, alimentația ecologică și proiectarea condițiilor de muncă și de recreere.

Noutatea şi originalitatea ştiinţifică: dezvoltarea unui program sistematic de îmbunătățire a funcționalității și adaptabilității sistemului senzorio-motor integrat pe baza examinărilor fundamentale

Rezultatele obținute care au determinat soluţionarea unei probleme ştiinţifice, aplicative, de importanţă majoră: a fost elaborat un model experimental complex de acțiune multimodală combinată a factorilor de mediu, au fost investigate reacțiile multicomponente ale organismului la condițiile ocupaţionale și a fost propus un program de acțiuni specifice privind neuroprotecția și neuroreabilitarea pentru menținerea viabilității și performanței resurselor umane.

Semnificaţia teoretică: dezvăluie interconectarea mecanismelor moleculare, tisulare și bioelectrice de neuroprotecție și neuroreabilitare.

Valoarea aplicativă: programul dezvoltat și testat în mod fundamental oferă din punct de vedere conceptual și strategic un algoritm de acțiuni menite să asigure restructurarea adaptivă a aparatului neuromuscular, care pune în aplicare activitățile profesionale și de viață cotidiană.

Implementarea rezultatelor ştiinţifice: în programe specializate pentru dezvoltarea copilului, adolescentului, adultului matur și reabilitare după tulburări de integrare senzorio-motorie și leziuni mintale și fizice.

ANNOTATION

Baciu Anatolie "Program of neuroprotection and neurorehabilitation based on the combined multimodal action of environmental factors, individual daily activity and ecological nutrition" Dissertation of Habilitated doctor in Biological Sciences, Chisinau, 2024.

Thesis structure: introduction, three parts, general conclusions and recommendations, 497 References, 5 annexes, 234 pages of basic text, 89 figures, 9 tables. The obtained results are published in 67 scientific papers on the thesis.

Keywords: environmental factors, adaptive remodeling, neuroplasticity, sensory-motor integration, sleep-wake cycle, neuromuscular functionality, body composition

Purpose: development of a fundamental scientific basis, experimental testing and application in health screening of occupationally active people under certain environmental conditions and a technological approach based on sensory-motor exercises under optimized conditions to prevent neurodegenerative diseases (Alzheimer, Parkinson)

Objectives: highlighting the basic mechanisms of the neuroprotective and neurorehabilitative action of the combination of multimodal environmental factors, promoting the functionality and adaptability of the integral sensory-motor system for optimization and balancing of gas exchange and blood circulation; applying a set of methods for experimental modeling and study of the personality-environment-occupation-performance model; fundamental testing of the neuromodulatory and neuroprotective action of brain monoaminergic systems triggered and maintained by environmental factors (hypoxia with hypercapnia), daily activity, sleep-wake cycle, ecological nutrition and design of work and recreation conditions.

Scientific novelty and originality: developing a systematic program to improve the functionality and adaptability of the integrated sensorimotor system based on fundamental examinations.

Results obtained that have led to the solution of a major scientific, applied problem: a complex experimental model of combined multimodal action of environmental factors was developed, the multicomponent reactions of the organism to occupational conditions were investigated and a program of specific actions on neuroprotection and neurorehabilitation was proposed for maintaining the viability and performance of human resources.

Theoretical significance: reveals the interconnected molecular, tissue and bioelectrical mechanisms of neuroprotection and neurorehabilitation.

Applicative value: The fundamentally developed and tested program conceptually and strategically offers an algorithm of actions designed to ensure the adaptive restructuring of the neuromuscular apparatus, which implements professional and daily life activities.

Implementation of scientific results: in specialized programs for child, adolescent, mature adult development and rehabilitation after sensory-motor integration disorders and mental and physical injuries.

АННОТАЦИЯ

Бачу Анатолий «Программа нейропротекции и нейрореабилитации, основанная на комбинированном мультимодальном действии факторов окружающей среды, индивидуальной ежедневной активности и экологическом питании», диссертация хабилитированного доктора биологических наук, Кишинев, 2024.

Структура диссертации: введение, три главы, общие выводы и практические рекомендации, библиография из 497 наименований, 5 приложений, 234 страницы основного текста, 89 рисунков, 9 таблиц. Результаты опубликованы в 67 научных работах.

Ключевые слова: факторы окружающей среды, адаптивное ремоделирование, нейропластичность, сенсорно-моторная интеграция, цикл сон-бодрствование, функциональность нервно-мышечного аппарата, состав тела

Цель работы: разработка фундаментальных научных основ, экспериментальная проверка и применение в скрининге функциональности профессионально активных людей в определенных условиях окружающей среды и технологического подхода, основанного на сенсорно-двигательных упражнениях в оптимизированных условиях для профилактики нейродегенеративных заболеваний (Альцгеймера, Паркинсона)

Задачи исследования: выделение основных механизмов нейропротекторного и нейрореабилитационного действия сочетания мультимодальных факторов среды, способствующих функциональности и адаптивности целостной сенсорно-моторной системы для оптимизации и балансировки газообмена и кровообращения; применение комплекса методов экспериментального моделирования и изучения модели «личность-среда-окружение-занятость-производительность»; фундаментальная проверка нейромодулирующего и нейропротекторного действия моноаминергических систем мозга, запускаемого и поддерживаемого факторами окружающей среды, суточной активностью, циклом сон-бодрствование, экологическим питанием и проектированием условий труда и отдыха.

Научная новизна и оригинальность: разработка на основе фундаментальных лабораторных испытаний систематизированной программы повышения функциональности и адаптабельности интегрированной сенсорно-моторной системы

Полученные результаты, которые привели к решению крупной научной и прикладной проблемы: разработана комплексная экспериментальная модель комбинированного мультимодального действия факторов окружающей среды, исследованы многокомпонентные реакции организма на профессиональных условия и предложена программа целенаправленных действий по нейропротекции и нейрореабилитации для сохранения жизнеспособности и работоспособности человеческого ресурса.

Теоретическая значимость: раскрывает взаимосвязанность молекулярных, тканевых и биоэлектрических механизмов нейропротекции и нейрореабилитации

Прикладное значение работы: разработанная и фундаментально протестированная программа концептуально и стратегически предоставляет алгоритм действий, целенаправленных на обеспечение адаптивных перестроек нервно-мышечного аппарата, реализующего профессиональную и бытовую повседневную жизнедеятельность

Внедрение научных результатов: в специализированные программы становления и развития ребенка, подростка, зрелого человека и реабилитации после нарушений сенсорно-моторной интеграции и травм ментальных и физических.

BACIU Anatolie

NEUROPROTECTION AND NEUROREHABILITATION PROGRAM BASED ON THE COMBINED MULTIMODAL ACTION OF ENVIRONMENTAL FACTORS, INDIVIDUAL DAILY ACTIVITY AND ECOLOGICAL NUTRITION

165.01 – HUMAN AND ANIMAL PHYSIOLOGY

Summary of the thesis of Habilitated Doctor in Biological Sciences

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