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## History of the creation and activity of the Functional Neurology Research Unit over 30 years

<sup>1</sup>Stela Odobescu, <sup>\*1</sup>Oxana Grosu, <sup>1</sup>Lilia Rotaru, <sup>1,2</sup>Victor Vovc, <sup>1</sup>Ion Moldovanu

<sup>1</sup>Functional Neurology Research Unit, *Diomid Gherman* Institute of Neurology and Neurosurgery

<sup>2</sup>Department of Human Physiology and Biophysics, *Nicolae Testemitanu* State University of Medicine and Pharmacy  
Chisinau, the Republic of Moldova

Authors' ORCID iDs, academic degrees and contribution are available at the end of the article

\*Corresponding author – Oxana Grosu, e-mail: [oxana.grosu.md@gmail.com](mailto:oxana.grosu.md@gmail.com)

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### Abstract

**Background:** The Functional Neurology Research Unit (FNRU) was created in 1992 at the State University of Medicine and Pharmacy of the Republic of Moldova. The activity of the scientific unit was essentially based on the concept of Functional Neurology, which was published in an article in the prestigious Italian journal *Functional Neurology* (1998) and continues to be further developed by Professors I. Moldovanu and V. Vovc.

**Conclusions:** Physiological aspects in the researches carried out by collaborators of the FNRU concerned research of breathing pattern, autonomic parameters of suprasedgmental and segmental level (research of heart rate variability, segmental vegetative samples, etc.), reactivity of cerebral vessels to modeled hypocapnia, trigeminal, somesthetic, visual, auditory evoked potentials in patients with chronic headache, etc. To conclude, the scientific objectives of the research carried out by the collaborators of the Functional Neurology Research Unit during 30 years of activity – the development of the problem of identifying and using the huge, so far still insufficiently researched possibilities of the “reserves” of the human brain for therapeutic purposes (treatment of chronic pain, movement disorders as a result of organic brain lesions, autonomic disorders, etc.) in the context of a new, modern and advanced understanding of the relationship and interaction of the human brain, psyche and body within a social background which is the essence of the *functional neurology*.

**Key words:** functional neurology, research, autonomic disorders, chronic pain

### Cite this article

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### Introduction

The Functional Neurology Research Unit (FNRU) was created in 1992 at the State University of Medicine and Pharmacy of the Republic of Moldova by the university professor, PhD in medical sciences Ion Moldovanu, who had previously worked for 11 years in Moscow in the team led by Professor Alexandr Vein. This laboratory was the only one of its kind in the former USSR, and its research was largely focused on functional neurological pathologies. After a two-year internship in France, Ion Moldovanu returned to Moldova.

The activity of the scientific unit was essentially based on the concept of Functional Neurology, a concept further developed by professors Ion Moldovanu as a neurologist, and Victor Vovc as a physiologist, based on both the clinical-physiological and the conceptual-theoretical approach, largely on the brilliant acquisitions of the Russian school of physiology (Anohin P. K., Bernstein N. A., etc.), which strongly influenced the development of neurology in general.

This concept, which was published in an article in the prestigious Italian journal *Functional Neurology* (1998)

[1], continues to be further developed by Professors I. Moldovanu and V. Vovc.

It should be noted that in the last 20 years neuroscientists have made an enormous leap forward in the study of the human brain. The scientific language relating to the nervous system has been enriched not only with new terms, but also with new concepts, thanks in large part to the appearance of remarkable investigative tools: computer tomography, magnetic resonance and, in particular, functional magnetic resonance, which has opened up unsuspected ways of penetrating the mysteries of the brain and the human psyche.

In 1997 Professor Ion Moldovanu also presented a comprehensive report on “Functional Neurology and its prospects for development” as a visiting professor at the Institute of Neurosciences in Paris (University of Paris VII). Of the 3 scientific monographs and 4 textbooks, in which Professor Ion Moldovanu is co-author, a reference manual for neurologists is worth mentioning: “Disorders of the autonomic nervous system”, a fundamental textbook, which has gone through 4 editions (last in 2010, edited in Moscow) [2].

Physiological aspects in the researches carried out by collaborators of the FNRU concerned research of breathing pattern, autonomic parameters of suprasedgmental and segmental level (research of heart rate variability, segmental vegetative samples, etc.), reactivity of cerebral vessels to modeled hypocapnia, trigeminal, somesthetic, visual, auditory evoked potentials in patients with chronic headache, etc.

It is important to mention that Professor Ion Moldovanu has succeeded in creating a consolidated team of researchers, who carry out a polyvalent study of autonomic (vegetative) disorders in different forms of neurological pathologies. He is rightly considered the founder of the local school of autonomic disorders.

The scientific directions of the research unit were established on the basis of the urgent needs of both clinical and scientific knowledge of Functional Neurology – a branch of modern neurology, which had not previously developed in the Republic of Moldova and which presents a comprehensive analysis of various functions in physiological or pathological conditions addressed to the functional system, to the relationship between voluntary and involuntary, as well as to the mechanisms of semantic regulation of concrete function. The “Functional Neurology” department included the research of headaches, different pain syndromes and pathologies from a pathogenetic, clinical and epidemiological point of view; and the areas of scientific activity of the Functional Neurology Research unit concerned the following compartments: primary and secondary headaches, chronic pain, segmental and suprasedgmental autonomic disorders, sleep disorders, movement disorders (Parkinson’s disease, Tourette’s syndrome, tics and others).

Functional neurological disorders (FND) are a common cause of disability and distress in neurological practice, being the second most common reason for consulting a neurologist after headache. Karina Bennett et al. performing an extensive review of publications on the prevalence and incidence of FND, found that they account for 5%-10% of neurological consultations internationally. Estimates of incidence are 12 per 100000 population per year. FND disproportionately affects women (approximately 3:1) [3].

Basically, the scientific research guided by university professors Ion Moldovanu and Victor Vovc focused on the study of the mind-body relationship [4]. This led to the specialization of the scientific research in the problems of the autonomic disorders (of the vegetative nervous system – involuntary and unconscious), but which are largely dependent on psychological processes (affective or emotional phenomena and motivational processes). After all a person, this ‘psycho-somatic’ being par excellence, being in the socio-cultural environment and being shaped by this environment, is in reality a bio-psycho-social being (George Engel, 1977) [5].

On the basis of the laboratory’s study directions, two Centres of Excellence were created: the Headache Centre (2010), the Somnology Centre (2013), three scientific

societies were founded: the Headache and Pain Society (president – Prof. Ion Moldovanu), the Psychoanalysis and Psychosomatics Association (president – Prof. Ion Moldovanu), the Sleep Medicine Society (president – Prof. Victor Vovc). Key collaborators of the research unit were and are: Ion Moldovanu, Victor Vovc, Stela Odobescu, Lilia Rotaru, Oxana Grosu, Adrian Lupusor et al.

**The scientific directions developed by the collaborators are:**

1. The problem of episodic, frequent and chronic pain in various forms of neurological, somatic and functional pathologies, in particular headaches (migraine, tension-type headache, trigeminal-autonomic headaches, etc.), extracephalic algic syndromes (fibromyalgia, dorsolumbalgia, visceral pain). Research has also been carried out on pain in Parkinson’s disease, multiple sclerosis, arterial hypertension, etc.

2. Pathology of the vegetative (autonomic) nervous system at both segmental and suprasedgmental (central) level. Functional neurological disorders (hyperventilation syndrome, panic attacks, syncopal (non-epileptic) states, sleep disorders, neurogenic tetany phenomena, neurological manifestations of hysterical conversion, etc.) were used as a model for study. Contributions have been made to the systematization of autonomic disorders conditioned by psychic factors and hyperventilation phenomena, revealing their role in various clinical structures.

**Argumentation of the scientific directions of the Functional Neurology Research Unit in fundamental aspect**

The clinical-morphological method of classical neurology, the method which laid the foundation for the great discoveries in neurology and which has retained its theoretical-practical value into the 21st century, did not always make it possible to explain clinical phenomena. For example, in Parkinson’s disease, a disease with established organic dysfunction, the patient can episodically completely get rid of the motor deficit existing in certain particular states (sleep, stress, emotions). Explanation of this phenomenon requires a broadening of the frontiers of the neurological discipline and can be approached partly in accordance with the concept of functional neurology.

Functional neurology (FN) attempts to overcome the limits of the clinic-morphological approach which are partly determined by the ‘organism-centrism’ of traditional concepts with the exclusion of the subject from the analysis of complex brain and mental mechanisms. Modern research has shown that there are ‘purely human’ mechanisms, absent in the animal behavioural model, which need to be taken into account.

The notion of *functional* itself can have several different meanings. For classical neurology the term “functional” was conceived as an antithesis of the notion of organic, i.e. organic damage to the nervous system. For example, J.-M. Charcot considered that in patients with hysteria manifested by pseudo-epileptic seizures, functional hemiplegia,

balance disorders without neurological signs, etc., the organic substrate was not detected and was conceptualised by the author as a “dynamic lesion” [6].

Another aspect of the term *functional* comes from the notion of “functional state of the brain”, a notion inspired directly from the framework of “activation theory” [7]. The functional state of the brain depends, according to the authors of this notion, on the level of activation of the brain. This approach, elaborated and further developed in the Moscow School of Neurology, for patients with Parkinson’s disease, contains the following emblematic statement: “Clinical and electrophysiological particularities ... are determined, on the one hand, by the lesional focus and, on the other, by the functional state of the brain”.

Another interpretation of the term *functional* in neurology can be related to the analysis of a specific function.

Thus, functional neurology presents a diverse spectrum of processes, functions in physiological or pathological conditions addressed to the functional system, the relationship between voluntary and involuntary, as well as the mechanisms of semantic regulation of the concrete function, investigated from a pathogenetic, clinical and epidemiological point of view [7].

#### **Autonomic (vegetative) disorders**

It is known that the autonomic nervous system together with the endocrine system are the main systems connecting to the psyche, the human brain and the body. Since Descartes the psyche (the soul – in Cartesian terms) and the human body have been conceived (and continue to be perceived today) as separate entities. This Cartesian dualism, being deeply implanted in Western concepts, persists, to the detriment of the integral, holistic approach of Eastern thought.

While in Moscow, then later in France, and continuing their scientific research in Moldova, Prof. I. Moldovanu together with Prof. V.Vovc studied functional disorders of the respiratory system in the context of affective and neuro-vegetative disorders, disorders of the cerebral control of the breathing pattern, the voluntary-involuntary relationship, the use of breathing as a method of treatment (respiratory biofeedback) and the induction of altered states of consciousness for therapeutic purposes [7]. As a major object of study, the respiratory dysfunctional syndrome – a distressing functional disorder, insufficiently known by physicians in their clinical work – was deeply investigated and analyzed.

In 1996 Prof. I. Moldovanu travelled to France together with Prof. V. Vovc as invited professors to carry out for 2 months a joint research with Professor Gila Benchetrit (head of the respiratory physiology laboratory of the Faculty of Medicine of the University “Joseph Fourier” in Grenoble, France), where breathing patterns in patients with Parkinson’s disease were recorded and analysed.

#### **The problem of chronic pain**

If acute, nociceptive pain really is a warning sign, then chronic pain is considered a neurological disease. The high

rate of chronic pain in the population leads scientists to consider chronic pain – a veritable pandemic. Chronic pain has become a public health problem because of its high prevalence, associated comorbidities and the disability it generates [8]. Analysis of pain prevalence varies from country to country, ranging from 2-40% [8, 9]. It is considered that globally 10% of the population is affected by chronic pain, i.e. 60 million people suffer from pain, and national and regional studies indicate prevalence of 20-25% [10]. In Europe 20% of people suffer from chronic pain, prevalence higher than 40% reported by Italy, France and Ukraine, i.e. every year 1 in 5 Europeans is affected by chronic pain [11]. Despite multiple researches conducted all over the world, chronic pain being usually very resistant does not give way, striking with great violence in the quality of human life [12].

In the Headache Centre of the *Diomid Gherman* Institute of Neurology and Neurosurgery about 65-70% of the patients who are referred suffer from chronic headache: migraine or tension-type headache (chronic headache is considered to be when the presence of headache is 15 or more days per month in the last 3 months). In the vast majority of these patients certain comorbidities are associated, which amplify and maintain the pain: medication abuse with analgesics, anxiety, depression, sleep disorders and multiple vegetative suprasedgmental and, less frequently, segmental disorders. A new, relatively recently recognised factor in the chronicity of pain is post-traumatic stress disorder, particularly the poor family atmosphere in childhood [13]. Consideration of comorbid illnesses, stresses, psychological states, etc. is necessary for an effective treatment.

A mixed study (quantitative and qualitative) was carried out in the framework of the master thesis in public health management of Mrs Oxana Grosu (scientific collaborator of Functional Neurology Reserch Unit), which included 355 patients, who completed a special questionnaire, the aim of the work being to analyze the management of the patient with chronic non-cancer pain in the health system of the Republic of Moldova. The results of the study showed the following: patients with chronic non-cancer pain are middle-aged, predominantly female, suffer from pain on average 10 years, with abuse medication, have failed drug treatment, having functional disability and are not satisfied with the management of chronic pain they receive in the health system. It is worth noting, that the chronic pain patient overburdens the health care system through visits to the family doctor and specialists, use of urgent care and frequent hospitalizations in the desire to receive the services they require [12, 14, 15].

The Functional Neurology Research unit’s team works together with colleagues from the Department of Neurology and the Department of Physiology of *Nicolae Testemitanu* State University of Medicine and Pharmacy (SUMPh) in the current project under the State Programme (2020-2023) which is specifically addressed to the study

of chronic pain with the theme: "Using 4P principles in the analysis of risk factors for the onset, perpetuation and progression of chronic pain" (20.80009.8007.01).

#### **Pain, autonomic nervous system dysfunction and somatic disturbances of a psychogenic nature**

Psychogenic pain or the psychogenic component of chronic pain is one of the problems still unresolved by algologists. In one third of patients with various pain disorders who come for neurological consultation, especially in patients with persistent pain associated with various comorbidities, the presence of a precarious, violent atmosphere is found both in the childhood period of the future adult and recent unhealthy relationships in the family or at work [13]. As a rule, patients do not realize the importance of this factor, and doctors unfortunately do not actively question patients on this topic. Working with patients suffering from chronic pain (headaches and pain in other locations) as well as psycho-vegetative disorders requires a special approach. Three principles need to be observed:

- 1) to identify the presence or absence of organic pathology;
- 2) to clarify the full range of the pain spectrum, the type of pain;
- 3) to elucidate the presence or absence of functional disorders.

Only a thorough investigation with an exhaustive anamnesis and a thorough analysis of psychological disorders, the use of a set of psychological performance tests can reveal the extent of psychological mechanisms, which generate pain. The use of the bio-psycho-social continuum paradigm is imperative in these cases.

#### **Consciousness and altered states of consciousness**

The brain has huge and largely unexplored reserves. Identifying and then using these reserves is one of the most important and promising ways for the development of further therapeutic strategies, not only in the field of neurology, but also for most existing pathologies. In recent years Prof. I. Moldovanu has succeeded in organizing an interdisciplinary research team (scientific researchers, residents, psychologists, students, etc.), which jointly conducted both the debate of various concepts and the research of certain brain functions, studied various altered states of consciousness - all this for a deeper understanding and application of the results obtained in the therapy of patients. A great success for the research was the collaboration with specialists in quantum physics of the Academy of Sciences of Moldova, namely on the same topic: the study of brain, consciousness and creativity from the point of view of modern quantum physics approaches and concepts [16].

#### **The development of non-pharmacologic therapeutic strategies**

Modern medicine is dominated by predominantly drug treatments, especially for chronic pain. The main idea of Prof. I. Moldovanu lies in the conviction that medical science does not make sufficient use of all the possibilities

offered by human nature. The treatment of chronic pain and autonomic disorders by non-pharmacologic methods is currently a fundamental and highly perspective goal in the world of therapies [17]. Recently, an important fact has been realized: the human brain can be compared to a mega-computer, which simultaneously processes a huge number of programs, manages dozens of biochemical „laboratories” of the body, influences complex neuro-physiological processes and makes various connections at both intracerebral and psycho-physiological (psychosomatic) levels. In the Functional Neurology Laboratory extensive research has been conducted on the use of transcranial electrical stimulation with direct current in non-pharmacologic therapy of chronic migraine [18], also - in the group of patients with chronic migraine and ventricular asymmetry, as well as beneficial results have been noted in the treatment of algic syndrome in patients with Parkinson's disease [19].

In the years of scientific activity of the Functional Neurology Research Unit several research projects have been carried out:

1. Multivariate study of cephalalgic, vegetative and extrapyramidal disorders. Epidemiological, pathogenetic and therapeutic aspects. 06.420.050F.
2. Preventive treatment of chronic migraine by transcranial direct current stimulation method. 10.820.05.10 GF.
3. Multivariate study of chronic pain in nervous system disorders. Epidemiological, pathogenetic, clinical, therapeutic and preventive aspects. 11.817.09.25A.
4. Research on chronic cephalic pain carried out in the Mayo Clinic, Department of Neurology, Arizona (USA) with Professor David Dodick in the framework of the Fulbright Program sponsored by the US Department of State (2002-2003, Ion Moldovanu, Stela Odobescu).
5. Epidemiological research on primary headaches in the Republic of Moldova funded by the International Headache Society (2005-2006) (Ion Moldovanu, Stela Odobescu, Lilia Rotaru, Oxana Grosu, Gabriela Pavlic).

Professor Ion Moldovanu has always been intrigued by the pathology of the autonomic nervous system, a complex, understudied field that was still developing. The leading specialist in the former USSR in this field, as well as in sleep medicine, was, at that time, Professor Alexander Vein from Moscow. Between 1980 and 1991 Mr Ion Moldovanu had the great opportunity to be a doctoral student and then a scientific collaborator in the Neurology Clinic of the Moscow Institute of Medicine „I.M. Secenov” (nowadays „I. M. Secenov” Moscow Medical Academy). A world-renowned scientist, well-known in the field of neuro-vegetative pathology, Prof. A. Vein succeeded in creating a highly scientific atmosphere in the research of the brain and the vegetative nervous system, as well as the human psyche, within a highly efficient team (10 professors and 20 medical doctors). The performance of this group was determined by the intersection of research from several disciplines: neurology, physiology, psychology, endocrinology. It was an innovative approach

at the time, it was new and fascinating. This allowed him to study not only clinical aspects of neuroscience, but also the fundamental science: neuro-physiology and especially psycho-physiology. In Moscow Mr Moldovanu defended two theses: "Neurogenic tetany syndrome" (1983) and "Neurogenic hyperventilation and vegetative disorders" (1991). Both theses were of great interest to neurologists because they were absolutely new, unstudied and unknown topics in the context of the pathology of the autonomic nervous system [20, 21].

These approaches, which Mr Moldovanu had learned in the team of Professor Alexandru Vein, were later transposed and developed in the research of the collaborators of the Functional Neurology research Unit, thus creating the first and the only laboratory of vegetology in the RM. The aforementioned aspects were also the target of the scientific research carried out by the collaborators of the laboratory - Victor Vovc, Stela Odobescu, Larisa Bobeico, Octavian Razlog, Ludmila Ciobanu, Severin Sohotchii, Gabriela Pavlic, Lilia Rotaru, Dorina Tiple, Oxana Grosu, Galina Corcea, Adrian Lupusor, Crsitina Chicu-Hadarca, etc.

In the Functional Neurology Research Unit, which later became part of the Institute of Neurology and Neurosurgery, researches in various aspects of functional neurology have been carried out over the years, most of which were scientific theses:

1. **Odobescu Stela.** Breathing pattern dysfunction in patients with vegetative suprasegmental disorders (clinical, psychological, neurophysiological and therapeutic study) (PhD).
2. **Ciobanu Ludmila.** Vegetative patterns in children of the first year of life (PhD).
3. **Siric Ala.** Neurogenic syncope in children (PhD).
4. **Tiple Dorina.** Specificity of vegetative disorders in patients with Parkinson's disease (PhD).
5. **Rotaru Lilia.** Chronic migraine in patients with cerebral ventricular asymmetry - clinical-electrophysiological and neuroimaging study (PhD).
6. **Corcea Galina.** Syncope in migraine patients - clinical and neurophysiological study (PhD).
7. **Maticiu Violeta.** Migraine as a risk factor in cerebral and coronary ischemia (PhD).
8. **Grosu Oxana.** Chronic migraine associated with arterial hypertension (PhD).
9. **Pavlic Gabriela.** Algic syndromes in patients with Parkinson's disease (PhD).
10. **Razlog Octavian.** Breathing pattern disorders in patients with panic attacks (PhD).
11. **Sidorenco Irina.** Peculiarities of neurophysiological indices changes under stress conditions (PhD).
12. **Besleaga Tudor.** Ventilatory and cardiac effects of voluntary hyperventilation - study in healthy volunteers and patients with panic disorder (PhD thesis by cotutelle).
13. **Profire Liliana.** Correlations of hormonal decline and psycho-vegetative disorders in menopausal patients (PhD).

14. **Plesca Viorica.** Autonomic disorders in children with irritable bowel syndrome (PhD).

15. **Curca Cristina.** Ophthalmological manifestations in patients with chronic migraine (PhD).

16. **Jubarca-Tulum Svetlana.** Clinical, psychological and neuro-vegetative peculiarities of pregnancy and birth in teenagers (PhD).

17. **Raileanu Gheorghe.** The role of perinatal factors in the clinical manifestations and pathogenesis of neuro-vegetative disorders in children (PhD2 - doctor habilitate thesis).

18. **Odobescu Stela.** Chronic migraine and associated autonomic disorders (epidemiological, clinico-neurophysiological and therapeutic study) (PhD2 - doctor habilitate thesis).

19. **Lozan Tatiana.** Epidemiological and medico-social aspects of primary headaches in adolescents (PhD).

Currently, the following theses are in progress, some even at the completion stage:

1. **Concescu Diana.** Analysis of the clinical profile of patients with post lumbar puncture headache and the therapeutic efficacy of blood-patch (PhD thesis carried out in cotutelle with the Headache Emergency Centre, Lariboisiere Hospital, Paris).

2. **Sajin Valeria.** Neuroanatomical correlation of tics and sensory phenomena in Gilles de la Tourette syndrome (PhD thesis carried out in cotutelle with the Department of Movement Disorders and Neuropsychiatry in Children and Adults, Institute of Neurogenetics, Luebeck, Germany).

3. **Lupușor Adrian.** Morning headache in patients with sleep-disordered breathing.

4. **Gavriliuc Olga.** Effect of deep brain stimulation on gait and posture disorders in patients with Parkinson's disease.

5. **Ganenco Andrei.** Relationship between heart and respiratory rhythms in healthy and panic attack patients.

6. **Lozovan Svetlana.** Psycho-physiology of respiratory paternity.

The research work has been carried out in international collaboration with numerous international institutions and scientific centres:

1. International Headache Society and the Russian language subcommittee (Prof. Zaza Katsarava) - methodology, research, academic exchange.

2. European Headache Federation - methodological support, research, academic exchange.

3. Russian Headache Society (Moscow) - methodology, research, academic exchange.

4. Italian Headache Society, Mondino Center for Head pain and adaptive disorders Pavia, Italy - research, academic exchange.

5. Headache Centre of the Neurology Department of the Roger Salengro University Clinic in Lille - Professor Christian Lucas - research, academic exchange.

6. The French Society for the Study of Migraine and Headache and the Headache Emergency Centre (Centre Urgences Cephalées), Lariboisière Municipal Hospital, Paris, France – research, academic exchange.

7. Department of Movement Disorders and Neuropsychiatry in Children and Adults, Institute of Neurogenetics, Luebeck, Germany – research, academic exchange.

8. Palliative Care Service of Malesroit (France) – promotion of the concept of palliative care in the public health care system in the Republic of Moldova by completing the university curriculum with this new discipline for the medicine of the Republic of Moldova.

9. Rehabilitation Clinic, Iasi, Romania – research, academic exchange.

10. Swiss National Scientific Foundation Centre – Scientific cooperation between Eastern Europe and Switzerland (SCOPES 2013-2016) – funding, methodological and logistic support, academic exchange.

11. Institute of Applied Physics, Laboratory of Quantum Optics of the ASM – research.

12. School of Public Health Management of *Nicolae Testemitanu* SUMPh – research, methodological support.

13. Department of Neurology and Physiology of *Nicolae Testemitanu* – research, academic exchange.

14. Doctoral School of *Nicolae Testemitanu* (SUMPh) – methodological and academic support.

A great influence for the advancement in the problem of pain and headaches had the scientific training in the Mayo Clinic Scottsdale (Arizona, USA) of Prof. Ion Moldovanu for 6 months (2002-2003). One of the scientific results of this stay was the publication of the monograph „Headache, facial and cervical pain” (authors – Moldovanu I., Dodick D., Odobescu S.), which was the first practical guide for the diagnosis and treatment of this neurological problem in the Republic of Moldova [22].

On the initiative of the director of the Institute of Neurology and Neurosurgery (INN), Prof. I. Moldovanu, inspired by this training, new performance centres in certain neurological fields were created within the INN. So, in 2010 the National Centre for Headache and Vegetative Disorders was created (head of the centre Stela Odobescu), in 2011 – the National Centre for Spinal Pain (head of the centre Svetlana Pleşca), and in 2013 – the National Centre for Sleep Medicine (head of the centre Ion Moldovanu).

For many years the Headache and Vegetative Disorders Centre associated with the Functional Neurology Research Unit, together with the Headache and Paroxysmal Disorders Department have played an essential role in promoting the knowledge of headaches, vegetative disorders, paroxysmal states both in the medical environment of the Republic of Moldova and for the population of our country.

#### **Main scientific results of the Functional Neurology Research Unit in the years of activity**

The first epidemiological study of primary headaches in the Republic of Moldova was conducted (I. Moldovanu, S. Odobescu, L. Rotaru, O. Grosu), which revealed the pre-

valence of episodic and chronic primary headaches in the urban and rural adult population [23], as well as among adolescents in Moldova (PhD thesis of Mrs Tatiana Lozan) [24, 25]. Prevalence data have been published internationally, and the study has been appreciated and mentioned by the International Headache Society and the European Headache Federation [23]. The overall prevalence of migraine, resulting from the first epidemiological study of primary headaches in the Republic of Moldova [23], is estimated at 20%: 16.5% for episodic migraine and 3.5% – for chronic migraine, i.e. higher than reported in most previous studies in Europe and the USA. Possibly this finding can be attributed to major social stresses, related to the period of socio-economic transition, through which Moldova is passing, and migraine, as it is known, is a disease sensitive to psycho-emotional disorders. The prevalence of chronic migraine of 3.5%, highlighted in this study, is also higher compared to most epidemiological studies conducted in the world so far [23].

The classification of headache disorders has been translated, implemented and disseminated in the Moldovan medical environment, being the first translation of this comprehensive and exhaustive diagnostic compendium in the field of headache in the European space [26].

There has been developed and proposed for use in scientific autonomic research the questionnaire Patient Vegetative Profile – a remarkable clinical tool, which elucidates polysystemically from the qualitative-structural and quantitative point of view 12 vegetative scales in patients with various organic and functional pathologies of the nervous system [27].

The role of risk factors (biological, psychological) in the manifestation and progression of chronic pain has been elucidated. The identification of biological (heart rate variability parameters, cardiovascular segmental vegetative evidence parameters, trigeminal evoked potentials, motor and somatosensor evoked potentials, blink reflex, etc.) and psychological markers important in the pathogenesis of chronic headaches has allowed a more precise differential diagnosis and the development of a more adjusted therapeutic strategy in chronic migraine [28].

Chronic migraine has been studied multilaterally – epidemiologically, neuro-physiologically, clinically and therapeutically (PhD2 thesis by Stela Odobescu) [28]. Thus, the specificity of autonomic regulation in the cardio-vascular system in patients with chronic migraine vs. frequent migraine was revealed by means of measurement of heart rate variability indices, namely, the impairment of vegetative balance with increased activity of the sympathetic nervous system and decreased activity of the parasympathetic nervous system, with indicators of amplification of the degree of centralization of autonomic heart rate regulation [29]. Neuro-physiological research of patients with chronic migraine by means of trigeminal evoked potentials has demonstrated a more pronounced activation of the functional state of the trigeminal system at different levels (nuclear-thalamic, thalamo-cortical) in the interictal period and

a tendency towards intensification of trigeminal system activity at the nuclear-thalamic level during migraine attack [30].

Various coping strategies and pain acceptance have been studied in patients with different forms of chronic pain (chronic migraine vs. chronic low back pain). The therapeutic approach of modifying the coping strategy (coping with pain) was implemented in the complex non-pharmacologic treatment of chronic headache syndromes, which contributed to decrease the expenses for abortive and preventive drugs of the chronic pain patient [31, 32].

Chronic migraine in association with asymmetry of the lateral cerebral ventricles has been investigated from an imaging, clinical and electrophysiological point of view (PhD thesis of Mrs Lilia Rotaru); the lateral cerebral ventricles asymmetry being proven as a factor influencing the severity of clinical manifestations in patients with chronic migraine. The increased degree of asymmetry of the lateral ventricles in patients with chronic migraine was associated with an earlier age of onset of headache, a longer duration of migraine attacks, a higher risk for the development of very severe and bilateral migraine attacks, and susceptibility to a greater number of triggers. Severe degree of ventricular asymmetry in patients with chronic migraine was more frequently associated with genetic predisposition for migraine (90%) and cutaneous allodynia (90%) [33-35].

A distinct clinical entity – syncopal migraine – was studied multilaterally (PhD thesis of Mrs Galina Corcea), which allowed to highlight the fact that patients with syncopal migraine and positive response to the tilt-test, compared to those who do not have syncope during migraine attacks, showed increased frequency and more severe intensity of migraine attacks, predominantly constrictive character of headache, increased frequency of syncopal attacks, shorter duration of premonitory symptoms, more profound degree of loss of consciousness, higher values on the vegetative motor profile scales and increased personality anxiety score [17, 36].

Chronic headache associated with hypertension was investigated (PhD thesis of Mrs Oxana Grosu), which demonstrated that hypertension amplifies the effect of migraine on the vascular wall leading to increased endothelial dysfunction of cerebral vessels. Another conclusion of the study is that subjects with chronic migraine and arterial hypertension present in 50% of cases a "non-dipping" circadian pattern suggesting an increased cardiovascular risk as this abnormal circadian pattern is associated with an elevated risk of stroke, cerebral white matter lesions, etc. [37, 38].

The relationship between migraine and cardiovascular and cerebrovascular pathology has been studied (PhD thesis of Mrs Violeta Maticiu), which allowed the establishment of a practical algorithm to identify the presence of migraine algic phenomenon in patients with acute vascular events (cerebral and cardiac). The severity of the ischemic stroke was evaluated depending on the presence or absence of migraine in these patients (according to the Ran-

kin scale). The study allowed to assess the peculiarities of the cephalalgic syndrome in patients with ischemic events (stroke and acute coronary syndrome). The weight of risk factors in patients with migraine and ischemic events (cerebral and coronary) was highlighted. Serum markers of endothelial dysfunction (nitric oxide metabolites) and oxidative stress were determined in patients with ischemic stroke and acute coronary syndrome with and without migraine. This research demonstrated that migraine has a serious contribution to the clinical and evolutionary manifestations of stroke and acute coronary syndrome by involving several pathogenetic mechanisms (oxidative stress, endothelial dysfunction). Thus, it has been shown that migraine is a true vascular risk factor for ischemic vascular events (cerebral and coronary) [39, 40].

An important pathogenetic aspect has been highlighted, that the presence of morning headache increases the likelihood that the patient has undiagnosed sleep apnea. The combination of psychological and biological factors triggers morning headache, which is a „red flag” for suspecting the presence of sleep-disordered breathing, the most common being Obstructive Sleep Apnea Syndrome, a known risk factor for sudden sleep death, myocardial infarction, hypertensive disease, excessive daytime sleepiness with falling asleep at the wheel, etc [41]. A very important research and investigation method – polysomnography – has been implemented in the clinical experience of INN (professor Victor Vovc, scientific collaborator Adrian Lupusor).

Respiratory dysfunctional syndrome (RDS), which plays a fundamental role in amplifying affective disorders, has been studied. Of all the mental phenomena, the most sensitive to respiratory dysfunction syndrome are the body sensation disorder and anxiety scales. The most pronounced vegetative disorders associated with RDS are cardiovascular disorders, vertigo-syncope and gastrointestinal disorders.

The specificity of the algic syndrome in patients with Parkinson's disease has been studied (PhD thesis of Mrs Gabriela Pavlic) [42], the importance of non-motor disorders in parkinsonian patients has been highlighted (PhD thesis of Mrs Dorina Tiple) [43], the neuro-physiological exploration of sensory phenomena in Tourette's syndrome and in patients with tics has been carried out. Multilateral research of patients with Parkinson's disease in association with chronic pain has allowed to highlight clinical features correlating pain with the severity of motor and non-motor signs, with predominance in patients with akinetic-rigid phenotype with more advanced dopaminergic deficit. The study provided support for the dopaminergic hypothesis in the pathogenesis of pain; the concept of clinical heterogeneity of the disease was confirmed by the association of pain-related variables and more severely expressed motor parameters with the akinetic-rigid phenotype of the disease [44]. Another area of movement disorders, such as tics has also been investigated – namely, the very complex relationship between subjective phenomena (desire for move-

ment – urge) and the actual movement (tic), which involve various brain systems and interact in a unitary way with each other, has been studied. The results of this study have allowed a deeper understanding of the pathogenetic mechanisms of tics, opening up real prospects for more effective treatment, both drug and non-drug (psychotherapy, bio-feedback, electrical stimulation, etc.) [45, 46].

Non-pharmacological treatment methods for chronic headaches using transcranial electrical stimulation with alternative and direct current have been implemented. Estimation of therapeutic efficacy of non-drug treatment method by transcranial electrical stimulation by means of serum beta-endorphin assessment (before and after treatment) contributed to the implementation of the method in clinical experience in pain control [47].

A set of powerful tests was developed, which allowed to identify vegetative (patient's vegetative-motor profile) and individual psychological parameters, in order to determine the patient's psycho-vegetative profile, with the aim of establishing an appropriate specific treatment.

The results of the study investigating the relationships between personality disorders and migraine or tension-type headache concluded that the patient's psycho-emotional background plays a very important role in the manifestation of primary headache and affective and vegetative disorders. As inflexible and maladaptive as personality traits are, so great is the subjective suffering and functional impairment. The patient's personality disorder negatively influences vegetative manifestations (accentuates respiratory dysfunction and somatoform disorders), affective manifestations (aggravates anxiety and depression), cephalalgic manifestations (increases duration of access, number of days per month with pain, use of analgesics).

Functional Neurology Research Unit collaborators have published more than 400 scientific papers in national and international scientific journals, registered 6 patents, participated in numerous European and world congresses in the field of pain, headache, extrapyramidal system pathology, as well as organized national scientific events with international participation. National and institutional clinical guidelines and protocols for the management of migraine, tension-type headache, Parkinson's disease, cognitive disorders, anxiety, depression, etc. have been elaborated and published.

Thus, a new field – *the vegetology of chronic pain* – has been developed, with elucidation of the role of the segmental and suprasegmental autonomic nervous system in the pathogenesis of frequent and chronic headaches.

If there was a task to formulate in a single sentence the scientific objectives of the research carried out by the collaborators of the Functional Neurology Laboratory during 30 years of activity – they would be the development of the problem of identifying and using the huge, so far still insufficiently researched possibilities of the “reserves” of the human brain for therapeutic purposes (treatment of chronic pain, movement disorders as a result of organic

brain lesions, autonomic disorders, etc. ) in the context of a new, modern and advanced understanding of the relationship and interaction of the human brain, psyche and body within a social background which is the essence of the *functional neurology*.

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**Authors' ORCID iDs and academic degrees**

Oxana Grosu, MD, PhD, Senior Researcher – <https://orcid.org/0000-0002-8677-372X>

Lilia Rotaru, MD, PhD, Associate Professor – <https://orcid.org/0000-0002-5340-5234>

Stela Odobescu, MD, PhD, Associate Professor – <https://orcid.org/0000-0001-8184-1220>

Victor Vovc, MD, PhD, Professor – <https://orcid.org/0000-0001-7624-9644>

Ion Moldovanu, MD, PhD, Professor – <https://orcid.org/0000-0002-1709-0319>

**Authors' contribution**

OG, LR, SO, VV, IM drafted the manuscript; VV, IM revised the manuscript critically. All the authors revised and approved the final version of the manuscript.

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**Ethics approval and consent to participate**

The research protocol was approved by the Research Ethic Board of the *Diomid Gherman* Institute of Neurology and Neurosurgery and the tests have been done according to the contemporary principles in biological standardization of experiences and Declaration of Helsinki with further amendments (Somerset West Amendment, 1996).

**Conflict of interests**

No competing interests were disclosed.

