

REVIEW

by

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Re: Dissertation on the topic “Evaluation of the Potential Therapeutic Benefits of Biofeedback Training as a Method for Reducing Stress and Improving the Mental Health of International Medical Students”.

Prepared and submitted by: Dr. Gabriela Georgieva Panayotova, full-time doctoral student in the “Pathophysiology” doctoral program, professional field 7.1.“Medicine”, Faculty of Medicine at Medical University “Prof. Dr. Paraskev Stoyanov” – Varna, for the award of the educational and scientific degree of “Doctor” (PhD).

By Order №R-109-238/July 30, 2026, of the Rector of the Medical University “Prof. Dr. Paraskev Stoyanov” – Varna (hereinafter MU-Varna), I have been appointed as a member of the scientific jury in the procedure for conferring the educational and scientific degree of “Doctor” (PhD) in the specialty of “Pathophysiology”, professional field 7.1.“Medicine”, and I have been designated to prepare this review. This evaluation is based on the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria, the Regulations for its Implementation, and the Regulations on the Development of Academic Staff at MU-Varna (hereinafter the “Regulations”).

1. ANALYSIS OF THE DOCTORAL STUDENT’S CAREER PROFILE

Dr. Gabriela Panayotova graduated from MU-Varna, where she earned a Master’s degree in Medicine in 2020. She subsequently earned two additional master’s degrees – in Health Management and Medico-Social Care (2022) and in Artificial Intelligence in Biomedicine (2025). Her academic career began in the Department of Physiology and Pathophysiology, Division of Physiology, Medical University of Varna, where, following a competitive selection procedure, she was appointed to the academic position of Assistant Professor in 2021. In 2023, she was enrolled

as a full-time doctoral student in the doctoral program in “Pathophysiology.” In 2025, she obtained a specialty qualification in “Physiology.” She completed specialized training in Global Clinical Research at Harvard Medical School (Boston, USA). She is a member of prominent professional and scientific organizations – the Bulgarian Medical Association, the Union of Scientists – Varna, the Bulgarian Society for Physiological Sciences, the American Physiological Society, the Asian Society for Pharmacology and Toxicology, and the International Organization of Psychophysiology.

2. GENERAL CHARACTERISTICS OF THE DISSERTATION

2.1. Relevance of the Problem

Medicine is one of the few fields in which substantial responsibilities and expectations are placed not only on practicing physicians but also on medical students. They are expected to master a large volume of facts and methods within a short period of time; while still relatively inexperienced, they are confronted with patients’ problems and suffering, and this inevitably requires sacrifices in their social and personal lives, leading to stress. Numerous studies worldwide have found that medical students, during their academic training, are more likely to experience psychological distress, anxiety, and depression (including more severe depression) than the general population. This adversely affects cognitive processes, leading to poorer academic performance and a reduced quality of life.

One aspect of globalization in today’s world is the free movement of people. This includes pursuing higher education abroad. For international students, this adds further challenges to the traditional stressors – alongside practical, financial, personal, and emotional difficulties, they must adapt to the cultural, linguistic, and social differences in the country where they study, as well as to the specific features of a different educational system.

Against this backdrop, the efforts of a number of research teams abroad to develop approaches and methods for coping with stress and preventing its harmful consequences among medical students seem logical. Psychological strategies dominate approaches to coping with and managing stress and overcoming its harmful effects, while the potential of psychophysiological approaches appears to receive less attention. These include biofeedback (BF) training, which is gaining increasing popularity worldwide.

In Bulgaria, data on the mental health of medical students are scarce. To date, no studies have been conducted on this issue among international students. The effectiveness of various strategies and methods for coping with and managing stress among medical students has not been analyzed.

All of the above provides grounds for asserting that the topic of this dissertation is timely, significant, and has high practical potential.

2.2. Aim and Objectives

The aim of this dissertation is clearly formulated on the basis of an analysis of what is known, as well as the uncertainties and gaps in current knowledge on the subject. The research undertaken to achieve the aim – “to evaluate the therapeutic potential of BF training as a method for reducing stress and improving the mental health of international medical students” – is logically structured into five research objectives, enabling the collection of psychometric data (on stress, anxiety, and depression) and physiological data (salivary cortisol and IgA), on the basis of which the therapeutic potential of heart rate variability-based biofeedback training can be interpreted.

The doctoral candidate has formulated three well-founded working hypotheses, which are to be confirmed or rejected based on the results obtained.

2.3. Length and Structure

The dissertation comprises a total of 186 pages – including text, figures, tables, and appendices. It is structured according to the standard sections recommended for a doctoral dissertation. The text is written in an appropriate scientific style and is clear and readable. It is effectively complemented and illustrated by 40 figures. The text does not unnecessarily duplicate the information presented in the 28 tables, which summarize the results. The list of references contains 645 sources.

3. EVALUATION OF THE CONTENT, METHODOLOGY, AND ANALYSIS OF THE RESULTS

3.1. Literature Review

The literature review draws on an impressive number of sources (645, all in English, most from the last 10 years), demonstrating the doctoral candidate’s desire to be as comprehensive and thorough as possible in presenting the research problem. The review logically begins with a discussion of stress. Due attention is given to its neurobiology, signaling pathways, effector axes, pathophysiology, and health consequences. Subsequently, depression and anxiety are discussed in

terms of their etiology, pathophysiology, clinical presentation, and prevalence. The second component of the literature review in the dissertation consists of data from studies on stress among international medical students – prevalence, causes, and consequences for mental health and academic performance. Separate sections are dedicated to anxiety and depression among medical students. The third component presents the nature, evolution, and current state of BF as a therapeutic method, with an emphasis on BF training based on heart rate variability. I believe that the literature review provides the necessary foundation and context for understanding the rationale, aim, objectives, and hypotheses of the study. The doctoral candidate demonstrates excellent knowledge of the scientific literature on the topic and the ability to select, organize, and analyze scientific information.

3.2. Research Methodology

The study conducted and presented in this dissertation has a sound experimental design (controlled longitudinal), and the methods used are appropriate for achieving the stated aim. The study examines the effect of BF training on levels of perceived stress, anxiety, depressive symptoms, psychophysiological reactivity, and biochemical markers of the stress response among international medical students, divided into two groups – a training group (24 participants with initially high baseline levels of stress, anxiety, and depression, enrolled in a BF training program) and a control group (23 participants who did not participate in the training program but underwent psychometric and psychophysiological assessments). This design allows the potential effect of BF training to be clearly delineated.

Four established, standardized, and widely validated psychometric instruments were used to assess the participants' psychological state: the Perceived Stress Scale, the Zung Self-Rating Anxiety Scale, the Beck Anxiety Inventory, and the Beck Depression Inventory.

Biofeedback training based on heart rate variability was conducted using the stationary emWave® Pro Plus system from the HeartMath® Institute, applying techniques standardized by the developer. The system provides heart rate variability data in the time and frequency domains: SDNN, RMSSD, pNN50, LF, HF, and the LF/HF ratio.

The physiological response to biofeedback training was assessed by measuring salivary cortisol and secretory immunoglobulin A (sIgA), which are recognized biomarkers of stress and psychophysiological reactivity. Cortisol was measured using an electrochemiluminescence

immunoassay (ECLIA), while salivary IgA was determined using a semi-quantitative enzyme-linked immunosorbent colorimetric assay (ELISA).

The Maastricht Acute Stress Test (MAST) was used to induce acute laboratory psychophysiological stress - a widely recognized and highly regarded laboratory protocol in psychoneuroendocrinology and psychophysiology for effectively inducing pronounced psychological and physiological stress.

The entire methodology is clearly and thoroughly described, ensuring transparency and reproducibility.

The statistical analysis is exceptionally comprehensive and in-depth, demonstrating the doctoral candidate's excellent data analysis skills. It was conducted using STATA version 18, Jamovi version 2.4.8, and GraphPad Prism version 5.0. Descriptive analysis, parametric and nonparametric comparative tests, repeated-measures ANOVA, and correlation analysis were employed. The selected statistical methods allow for a comprehensive and integrated approach to data analysis, combining descriptive, comparative, longitudinal, and multivariate approaches for a valid interpretation of the therapeutic effects of BF training on the mental and physiological status of the participants.

3.3. Results and Analysis

The results are presented in a detailed, clear, and consistent manner. The tables are well organized. The figures effectively illustrate the results and further aid in their understanding. The analysis of the results is focused and appropriately contextualized within the existing scientific literature—consistencies are highlighted, discrepancies are noted along with possible explanations, and excessive or unfounded interpretations are avoided. In the discussion, the doctoral candidate demonstrates analytical and critical thinking. This approach leads to a concise and informative conclusion that:

- The applied BF program has the most pronounced effect on the participants' psycho-emotional state;
- Adaptation to BF training is a complex and nonlinear process of autonomic reorganization and stabilization that cannot be assessed using a single heart rate variability parameter, but rather through a comprehensive analysis of heart rate variability parameters;

- Although salivary cortisol and IgA showed minimal changes over the course of the training program, there are associations between the early post-stress cortisol response and anxiety, as well as between changes in cortisol and secretory IgA, suggesting their involvement in the stress response;
- Heart rate variability measures have a higher predictive value for improvement in overall mental state compared to the biochemical markers examined;
- There is heterogeneity in the relationships between psychometric results, heart rate variability measures, and laboratory markers (cortisol and salivary IgA), indicating that a single physiological measure cannot fully describe the psychophysiological response to stress and the BF training program.

4. EVALUATION OF CONTRIBUTIONS

I accept the doctoral candidate's self-assessment of the contributions of her dissertation – seven original contributions and four confirmatory contributions. I would like to highlight that:

- This is the first controlled longitudinal study in Bulgaria on the effect of BF training based on heart rate variability in international medical students, combining psychological, autonomic, and biochemical indicators of the stress response;
- A structured protocol for BF training based on heart rate variability was developed, along with a model for psychophysiological monitoring of the individual response to BF training, in which data from psychometric measurements are analyzed in conjunction with indicators of heart rate variability, salivary cortisol, and IgA;
- Comparative modeling of the prognostic value of heart rate variability measures, salivary cortisol, and secretory IgA with regard to changes in psychophysiological status was performed, demonstrating the greater informativeness of baseline heart rate variability profile measures in predicting improvements in perceived stress and anxiety;
- A methodological foundation has been established for future multidisciplinary studies on stress and self-regulation, combining psychometric assessment, heart rate variability analysis, and the examination of hormonal and immunological markers.

- The results obtained provide grounds for recommending that BF training based on heart rate variability become part of systematic strategies for preventing stress and mental exhaustion among medical students, with university health and psychological centers integrating BF sessions as a form of psychophysiological prevention.

5. EVALUATION OF PUBLICATIONS

The results of the dissertation are reflected in three scientific publications and four scientific reports, demonstrating the successful dissemination of the scientific and applied contributions of the work, including in reputable journals. Two of the publications are in the *Journal of IMAB* (Web of Science, IF 0.2), and one is in *Scripta Scientifica Medica* (National Reference List). The abstracts of the scientific communications were published in scientific journals indexed in internationally recognized scientific databases – two in *Acta Physiologica* (Web of Science, IF 5.7; Scopus, SJR 1.528) and two in the *International Journal of Psychophysiology* (Web of Science, IF 3.3; Scopus, SJR 0.982). The doctoral candidate is the first author of all publications and scientific reports.

6. CRITICAL COMMENTS AND RECOMMENDATIONS

I believe that the stated aim, objectives, and working hypotheses would be even better substantiated if the doctoral candidate had included a brief section titled “Conclusions from the Literature Review” at the end of the literature review.

7. CONCLUSION

The presented dissertation constitutes a complete, independent, and methodologically sound scientific study with clear scientific value and indisputable contributions – it contributes to clarifying the potential of BF training based on heart rate variability as a non-pharmacological method for reducing stress and improving mental health among international medical students. The doctoral candidate demonstrates the scientific knowledge and skills necessary to conduct independent research – from assessing the significance of a scientific problem and formulating a scientific idea to designing, planning, and conducting studies, followed by critical analysis of the results obtained. The recommendations I have made in no way diminish the merits of the dissertation. The dissertation meets the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria, the Regulations for its Implementation, and the Regulations on the Development of Academic Staff at MU-Varna. In light of the foregoing, I give a positive

evaluation of the dissertation and of the doctoral candidate's qualities as a researcher and vote "FOR" the conferral of the educational and scientific degree "Doctor" (PhD) in the specialty "Pathophysiology", professional field 7.1. "Medicine", upon Dr. Gabriela Georgieva Panayotova.

Заличено на основание чл. 5,
§1, б. „В“ от Регламент (ЕС)
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Prof. Zlatislav Stoyanov, MD, PhD, DSc

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