



REVIEW

By Prof. Georgi Panov Panov, MD, PhD, DSc

Head of Clinic at UMHAT “Prof. Dr. Stoyan Kirkovich”

External member of the Scientific Jury, appointed by Order No. P-1756/06.06.2024 of the Rector of the Medical University Plovdiv

In the procedure for the defence of a dissertation for the award of the educational and scientific degree 'Doctor', professional field 7.1. "Medicine", doctoral programme "PSYCHIATRY"

Author: Anna Aleksandrova Todeva-Radneva, MD

Form of the PhD: independent training

Department: Psychiatry and Medical Psychology, Faculty of Medicine, MU Plovdiv

Topic: „Translational cross-validation of neuroimaging and molecular biomarkers in the differential diagnosis of unipolar and bipolar depression”

Scientific supervisor: Assoc. prof. Sevdalina Kandilarova, MD, PhD, MU Plovdiv

Consultant: Priv.-Doz. Ronald Sladky, PhD

1. General presentation of the procedure and the PhD student

The submitted set of materials on electronic media is in accordance with Article 70 (1) of Section I. Acquisition of educational and scientific degree "DOCTOR" and scientific degree "DOCTOR OF SCIENCES" at MU-Plovdiv; Regulations of MU-Plovdiv from 28.01.2021 and includes all required documents. The structure of the dissertation complies with the rules for the preparation of a dissertation with an optimal balance between its different parts. Dr. Todeva-Radneva has submitted three scientific publications in journals with impact factor and participation in five scientific forums.

2. Brief biographical data about the PhD student

Dr. Todeva-Radneva was born on August 31, 1992. She graduated from "Ivan Vazov" secondary school, Plovdiv in 2011 and from the Medical University - Plovdiv in 2017. Her professional experience includes working as a resident at: the St. Mina Hospital, Internal Diseases Department, Plovdiv; Multiprofile Transport Hospital, Internal Diseases Department and assistant professor at the Department of Psychiatry and Medical Psychology at MU-Plovdiv. At present she is a teacher at the Department of Psychiatry and Medical Psychology, Medical University Plovdiv and a specializing doctor in Psychiatry at the Clinic of Psychiatry at UMHAT "St. George", Plovdiv. She has also been part of the team of two national projects and participated in various training courses. She has research interests in the field of translational neuroscience, neuroimaging and affective disorders.

3. Relevance of the topic and appropriateness of the aims and objectives

The topic of this dissertation is extremely current given the increasing prevalence of mental illness, including affective disorders, and the lack of objective clinical diagnostic methods. Some of the major problems in clinical psychiatric practice include subjective assessment methods, lack of diagnostic biomarkers, and inadequate therapeutic efficacy of psychiatric disorders, including affective disorders. Furthermore, differentiating major depressive disorder and bipolar disorder in a current depressive episode remains challenging due to overlapping symptomatology. At present, many studies are focusing specifically on elucidating the etiopathogenetic mechanisms of MDD and BD, and a multifactorial genesis of these disorders has been established, including genetic, epigenetic, immunological, oxidative and nitrosative stress, neurobiological, and other factors. Dr. Todeva-Radneva successfully applied innovative methods and a multidisciplinary approach to the study of several etiopathogenetic factors, which highlights the relevance of her dissertation.

The research objective is logically deduced from the described hypotheses. The tasks described are relevant to the aim and the planned study.

4. Expertise on the problem

The PhD student demonstrates a thorough knowledge of the problem by reviewing recent research and incorporating it into the dissertation literature review. It is clearly written, and current data on the etiopathogenesis of affective disorders are systematized in the context of neuroimaging,

neurobiological, neuroimmunological, and other findings. It is pointed out that the available heterogeneity of data hinders a much-needed change in the nosological nomenclature and diagnostic and therapeutic approaches to mood disorders. The PhD student successfully summarizes the existing problems, emphasizes the need to apply complex and multidisciplinary approaches and proposes scientifically sound solutions.

5. Research methodology

The methods of the study are described precisely and specifically and are chosen according to the stated aim and objectives. The study has three components: Analysis of retrospective neuroimaging data (resting-state fMRI) performed in a sample of 103 individuals, including 43 healthy controls, 35 MDD patients, and 25 BD patients; analysis of prospective data from a sample of 78 individuals, including 40 healthy controls, 23 MDD patients, and 15 BD patients; and laboratory testing of expression levels of certain long-noncoding RNAs and microRNAs, which was performed in a reduced sample. All studies were approved by the Ethics Committee of the Medical University of Plovdiv. For translational purposes, it would be advantageous to have a concordant sample in which both neuroimaging and molecular biological markers were studied.

6. Characteristics and contribution of the thesis

The dissertation is written at a high scientific level and meets all regulatory requirements. The results are illustrated with 16 figures and 11 tables. The conclusions drawn are based on a thorough analysis and correspond to the set tasks. Aberrations of functional connectivity of regions related to cognitive, psychomotor, emotional and volitional functions were found that could distinguish unipolar from bipolar depression. The results of the direct comparison between MDD and BD showed a statistically significant hyperconnectivity of the anterior cingulate cortex with the left cerebellar cruri in MDD that was not observed in bipolar depression. In addition, the prospective study found that when performing a cognitive task with emotional distractors in the neutral distractors>no distractors contrast, hyperactivity of the right lingual gyrus, the right occipital fusiform gyrus, and the right external cerebellum was observed in BD but not in MDD. This result also indicates the potential of altered cerebellar activity during a cognitive task as a possible marker to distinguish unipolar from bipolar depression, but this would need to be confirmed in a larger and independent sample. On the other hand, there was no statistically significant difference in the

expression of the microRNAs examined between the MDD and BD groups, confirming the existence of common mechanisms of these disorders.

I accept the contributions mentioned by the doctoral candidate:

- Theoretical-methodological:
 - A new paradigm for the study of cognitive functions with emotional distractors has been developed and validated, with the potential for translation to a clinical assessment tool by quantitatively indexing responses/assessing success rates in the subjects.
 - An interdisciplinary approach has been applied, through which more data have been accumulated to help elucidate the pathogenesis of affective disorders.
- Research Applications:
 - Evidence was generated for the role of altered anterior cingulate cortex and cerebellar peduncle connectivity as a possible differentiating marker in unipolar and bipolar depression.
 - Pilot data have been generated on the potential of examining cerebellar activity during a task engaging cognition as a possible differentiating marker in unipolar and bipolar depression.
 - Pilot data have been generated for the potential establishment of molecular biological biomarkers for the diagnosis and monitoring of treatment response in affective disorders.

Dr. Todeva-Radneva's work contributes to the expansion of knowledge in the field of psychiatry and offers new opportunities for differential diagnosis of unipolar and bipolar depression.

7. Evaluation of publications and personal contributions

Dr. Todeva-Radneva is the author of three scientific articles in international journals with impact factor and has participated in five scientific forums. She is the first author of all presented articles. All of the presented materials show the personal involvement of the PhD student in the development and implementation of the study.

8. Abstract

The abstract meets the requirements and illustrates the main results of the study. It is 54 pages long and its structure reflects that of the dissertation.

9. Critical comments and recommendations

My recommendations relate to the need to validate the present study in a larger and concordant sample by not only expanding the panel of molecular markers but also accounting for the effect of the pharmacotherapy administered.

CONCLUSION

The dissertation contains scientific and applied results that represent an original contribution to science and meet all the requirements of the Law for the Development of Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for the Implementation of the LDASRB and the relevant Regulations of the Medical University - Plovdiv. The submitted materials and dissertation results fully comply with the specific requirements of MU - Plovdiv.

The dissertation work shows that the PhD candidate Dr. Anna Todeva-Radneva possesses in-depth theoretical knowledge and professional skills in the scientific specialty of Psychiatry demonstrating qualities and skills for independent scientific research.

Due to the foregoing, I confidently give my positive evaluation of the research conducted, as represented by the above-reviewed dissertation, abstract, results and contributions, and propose to the Honorable Scientific Jury to award the degree of 'Doctor of Education and Science' to Dr. Anna Todeva-Radneva in the Doctoral Program in Psychiatry.

Reviewer:


/Prof. Dr. G. Panov, MD, PhD, DSc/

Заличено на основание
Чл.5 §1, б. "В" Регламент (ЕС)2016/679