

STATEMENT



By Prof. Dora Konstantinova Zlatareva, MD, PhD
Head of Department of Diagnostic Imaging, Medical Faculty,
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Member of Jury designated by a written order № P-1756/06.06.2024г
of the Rector of the Medical University Plovdiv

On dissertation for awarding the educational and scientific degree of **Doctor**

Author: Anna Alexandrova Todeva-Radneva, MD

Mode of PhD student: independent preparation

Department: Psychiatry and medical psychology MF, MU-Plovdiv

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

Scientific Supervisor: Associate Professor Dr. Sevdalina Kandilarova, MD, Medical University – Plovdiv

Consultant: Priv.-Doz. Ronald Sladky, PhD

1. General presentation of the procedure and the PhD student

The set of materials submitted by the candidate on electronic media is in accordance with Article 115 (1) of the Procedure for Acquisition of the PhD Degree at MU - Plovdiv; Regulations of MU-Plovdiv of 06.11.2014 and includes the required documents.

The PhD student has submitted 3 scientific articles in journals with impact factor and 5 participations in scientific forums.

Biographical information and career development

Dr. Anna Alexandrova Todeva-Radneva was born on 3.1.1992. In 2011 she graduated from the Ivan Vazov Medical School in Plovdiv, Bulgaria. In the period from 01.11.2017-30.05.2018 she worked as a doctor - assistant therapist in the hospital "St. Mina" Ltd, Internal Diseases Department, Plovdiv. From 06/2018-06/2020 - Doctor - Resident at the Department of Internal Diseases, Multiprofile Transport Hospital, Plovdiv. From 11.02.2019-31.01.2024 Dr Todeva is an assistant professor at the Department of Psychiatry and Medical Psychology, Plovdiv Medical University, and from 31.1.2024 to the present she is a lecturer at the same university. Since 1.1.2021 she is a specialist in psychiatry at the Clinic of Psychiatry, University Hospital "St. George". The PhD student is part of the team of two national projects under the National Programme "European Scientific Networks". Her research interests focus on translational neuroscience; psychiatry; neuroimaging - functional magnetic resonance imaging and magnetic resonance spectroscopy; neurobiological constellations in affective disorders; and clinical neuropsychology. The doctoral candidate has participated in various training courses in the country and abroad, during which she became familiar with the world achievements in the field of research. Dr Todeva-Radneva is fluent in English and Russian and has excellent computer skills.

2. Current relevance

The topic is characterized by current relevance due to the increasing prevalence of mental illnesses, particularly affective disorders, and the lack of standard objective clinical diagnostic methods and validation by evidence-based methods. Effective biomarkers for early diagnosis of these disorders have not been established, and drug treatment in many cases does not result in recovery or relapse prevention in several disorders. Many studies aim to improve our knowledge of the aetiopathogenesis, diagnosis and treatment of GD and BD. On the other hand, the distinction between unipolar and bipolar depression remains a major problem for clinicians because of the almost complete overlap in clinical symptomatology between the two disorders.

Magnetic resonance neuroimaging, especially functional neuroimaging, and the methods of molecular biology, neurobiology and neuropharmacology are appropriate tools to achieve this goal. The focus of modern psychiatry is on a translational approach to neuroscience and the search for

objective biomarkers that allow a clear distinction between norm and pathology as well as between different psychopathological changes.

Dr Todeva-Radneva uses non-invasive biomarkers through functional magnetic resonance imaging and state-of-the-art molecular laboratory methods through a multidisciplinary approach, applying the translational approach, which again confirms the relevance and importance of the thesis.

3. Knowledge of the problem

The doctoral candidate is very familiar with the state of the problem and the changes in knowledge in recent years. The literature review is written in an excellent scientific style. The historical background in modern psychiatry for the emergence of the conceptualisation of psychiatric disorders, the structural and functional MRI changes in major depressive disorder and bipolar disorder, and the role of genetic and epigenetic factors in the aetiopathophysiology of affective disorders are presented. At the end of the literature review, Dr Todeva has presented a summary of the existing problems, the need to enrich the knowledge in this field and the scientific potential of future research on the topic of the dissertation.

4. Methodology of the study

The total number of patients studied was 1 each. For the first component of the study, the available data (from two modalities: structural and resting fMRI) were analysed, with the final sample consisting of 103 individuals divided into groups as follows. For the second component, the final sample consisted of 78 individuals divided into groups as follows: WC = 40 individuals, GDR = 23 individuals, BR = 15 individuals. The participants were from the Psychiatric Clinic of St. George University Hospital, Plovdiv, DPB Pazardzhik, CDC Plovdiv and outpatients. Functional and structural MRI were performed at the Centre for Translational Neuroscience, Plovdiv Medical University. The patient population and the inclusion and exclusion criteria are described in detail in order to ensure that the study objectives are met. In addition to clinical methods, state-of-the-art laboratory methods are used, and magnetic resonance imaging is performed on a 3 Tesla machine, which provides the highest quality structural images and detailed information from functional

scanning. The methods used are described in detail to allow future replication of the study and comparison with results from other teams. Statistical methods and processing software have been skilfully chosen to guarantee the reliability of the results obtained. The research methodology chosen by Dr Todeva-Radneva is modern and allows to reach the set goal and to obtain an adequate answer to the tasks of the dissertation.

5. Characteristics and evaluation of theses and contributions

The thesis consists of 122 pages, 16 figures and 11 tables. The dissertation complies with the requirements of MU-Plovdiv in terms of structure and volume content. The bibliography, which is up-to-date and comprehensive, contains 246 references in Latin.

The thesis is structured in the following sections: introduction, literature review, aim and objectives, research questions, methods, results, discussion, conclusions, contributions, bibliography. The technical layout of the thesis meets the requirements.

As a result of the review, a clear aim is logically derived - to investigate the differential diagnostic potential of neuroimaging and molecular markers in patients with unipolar and bipolar depression. The 3 objectives are consistent and scientifically justified. They will be achieved step by step during the study. The study consists of 2 parts: 1. Application of new statistical methods to process already collected neuroimaging data; 2. Implementation of a newly developed fMRI paradigm in an independent sample.

The results of the study are presented in 4 sections. Demographic and clinical characteristics; 2. Results of neuroimaging data analysis of the retrospective sample; 3. Results of neuroimaging data analysis of the prospective sample; 4. Results of molecular biological analyses. The PhD student identified changes in functional connectivity of the anterior cingulate cortex and right anterior insula in patients with depression compared to healthy controls. According to the results, increased functional connectivity between the anterior cingulate cortex and the cerebellar peduncles could differentiate GAD from PD. An interesting finding is that altered activity in certain brain areas during a task involving attention and short-term memory could distinguish unipolar from bipolar depression.

Altered activity was found in GDR and BR primarily in regions involved in cognitive and regulatory processes. Differential expression of microRNAs directly related to the processes of

neurodevelopment, neurogenesis, neurodegeneration and neuroinflammation was found in patients with depression. The study shows that there is no significant difference in the expression of the microRNAs studied in GAD and PD.

Some of the results contribute to a better biological understanding of the aetiology of affective disorders and improve the therapeutic approach.

In the Discussion section, Dr Todeva-Radneva compares her data with the known literature, demonstrating a thorough knowledge of the problem and critical analysis. The differences are outlined and scientifically sound hypotheses for their existence are proposed. The 8 conclusions are based on the literature review, analysis of own results and discussion. They are accurately formulated and reflect the tasks set and the results obtained.

I fully accept the contributions mentioned by the PhD student. The theoretical and methodological contributions are the development and validation of a new paradigm for the study of cognitive functions with emotional distractors, as well as the application of an interdisciplinary translational approach to accumulate more data to help clarify the aetiopathogenesis of affective disorders. In terms of scientific application, according to the doctoral candidate, the following contributions will be made

- Evidence has been provided for the role of altered connectivity of the anterior cingulate cortex and cerebellar peduncles as a possible discriminator of unipolar and bipolar depression.
- Pilot data were generated on the potential of examining cerebellar activity during a cognitive task as a possible discriminator of unipolar and bipolar depression.
- Pilot data have been generated for the potential establishment of molecular biomarkers for the diagnosis and monitoring of treatment response in affective disorders.

6. Assessment of publications and personal contribution of the doctoral candidate

On the topic of the dissertation, Dr Todeva-Radneva has submitted 3 scientific articles in peer-reviewed journals with impact factor and 5 participations in scientific forums. The doctoral candidate is the first author of each of these articles. The scientific activity of Dr Todeva-Radneva exceeds the minimum scientific metrics for a PhD according to the requirements of the current law on PhD and the regulations of MU-Plovdiv.

Dr Todeva-Radneva's personal involvement is evident from the text of the thesis, the abstract and the publications presented.

I have no critical comments or recommendations about the research and materials presented.

7. The author's abstract

The abstract reflects the essence of the dissertation and meets the requirements. It is presented in 54 pages and consists of parts that present the structure and content, main results and contributions of the dissertation.

CONCLUSION

I am of the opinion that the presented doctoral thesis of Dr Anna Alexandrova Todeva-Radneva is up-to-date, has been carried out using the most modern imaging and laboratory research methods, and makes original theoretical-methodological and scientific-applied contributions to modern psychiatry. The structure, content and volume meet all regulatory requirements of the Academic Staff Development Act (ASDA) in the Republic of Bulgaria, Regulations for implementation of ASDA and Regulations of Medical University – Plovdiv. The presented materials and the results fully comply with the specific requirements adopted in connection with the Regulations of MU - Plovdiv for application of ASDA.

The dissertation shows that the doctoral candidate Anna Alexandrova Todeva-Radneva possesses in-depth theoretical knowledge and professional skills in the scientific field of psychiatry, demonstrating qualities and abilities for independent scientific research.

Based on the above, I confidently give my positive assessment of the research conducted, presented in the above reviewed dissertation, abstract, post-dissertation results and contributions, and propose to the esteemed scientific jury to award the educational and scientific degree of "Doctor" to Dr. Anna Alexandrova Todeva-Radneva in the doctoral programme "Psychiatry".

8.8. 2024 г.

Prof. Dora Konstantinova Zlatareva, MD, PhD

Sofia

 Заличено на основание
Чл.5 §1, 6, "В" Регламент (ЕС)2016/679