

STATEMENT OF EVALUATION

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SUBJECT: Dissertation for the acquisition of a scientific and educational degree "Doctor" (PhD) in the professional field of Medicine, specialty Psychiatry, entitled:

TRANSLATIONAL CROSS-VALIDATION OF NEUROIMAGING AND MOLECULAR BIOMARKERS IN THE DIFFERENTIAL DIAGNOSIS OF UNIPOLAR AND BIPOLAR DEPRESSION

PhD candidate: *Anna Todeva-Radneva MD*

1. General presentation of the procedure and the PhD student

The presented set of paper/electronic materials **is** in accordance with the normative acts at the legislative and regulatory level; the regulations under the Procedure for Acquiring the Doctoral Degree at MU-Plovdiv; Regulations for the Academic Development of MU-Plovdiv

2. Topicality of the theme

The dissertation of Anna Todeva-Radneva is dedicated to a topic that is especially relevant in neuropsychiatry. The classical dichotomy of unipolar and bipolar clinical forms of depression, enriched with atypical and transient syndromes, presents a challenge for both clinical decision-making and the determination of the underlying mechanisms of the disease through biomedical measurements. There are a large number of studies at the molecular level and at the level of brain imaging, but nevertheless there are opportunities for new and different syncretic approaches that bring together methodological perspectives and searches. In-depth consideration of affective disorders through models of brain connectivity at rest, as well as through task-based measurements, has recently been successfully combined with molecular, genetic, epigenetic, immunobiochemical assessment methods.

3. Background knowledge of the problem

The PhD student has state-of-the art knowledge of the problem and critically evaluates the literature. Within the framework of the literature review, a comprehensive presentation and analysis of theoretical concepts regarding existing explanatory models and pathogenetic mechanisms are delivered. Achievements in the field of translational knowledge through interdisciplinary studies of cognitive and affective processes are reflected. The relationship of the factors under consideration with the subject of the dissertation is indicated.

4. Methodology of the study

The set of research methods allows achieving the set goal and obtaining an adequate response to the problems addressed in the dissertation. The author has developed the methodological toolkit under the supervision of the scientific consultant Assoc. Prof. Dr. Ronald Sladki (University of Vienna). Her dissertation is among the significant achievements of the project "*Development of Institutional Partnership in the Field of Neuroscience*", funded by the National Program "European Research Networks", funded by the Ministry of Education and Science on the basis of good or very good evaluation of project proposals under the Twinning Program of the European Commission.

In this regard, Dr. Todeva has conducted long-term specializations at the University of Vienna in the period 2020-2023. Her approach is distinguished by its meticulousness and sensitivity to quality control.

5. Characteristics and evaluation of the dissertation and contributions

The dissertation is structured in three segments.

The first is a study of functional connectivity at rest in a retrospective sample composed of patients with recurrent depressive disorder, depression in the context of bipolar illness, and healthy controls. Its results show significant increase of functional connectivity between the anterior cingulate cortex and the primary somatosensory and motor cortex, as well as the superior parietal lobule, precuneus and right lateral occipital cortex in all patients with depressive syndrome compared to healthy controls. Alterations in the functional connectivity of the anterior cingulate cortex and of the right anterior insula have been found in patients with depression from healthy controls, which could explain some of the cognitive, psychomotor, emotional and volitional disorders observed in the phenomenology of both affective disorders. Evidence is presented in favor of the statement that increased functional connectivity between the anterior cingulate cortex and the cerebellar feet could distinguish major depressive disorder from bipolar disease.

These data contradict my own beliefs as a scientist and clinician who adheres to the continuum theory in mental illness. Nevertheless, I feel proud that a scientist from the group I lead has the consistency and critical thinking to express and defend her disagreement.

The second segment is a prospective sample study using task-based functional MRI. The latter is an original modification of the image author from the International Affective Pictures System, designed to evaluate affective interference in cognitive processes. The activation of structures responsible for both the processing of visual stimuli and basic cognitive and socio-cognitive functions such as attention, memory, decision making, abstract thinking, response to social stimuli in the three groups studied: health controls, major depressive disorder and bipolar disease in all contrasts studied has been demonstrated. Some of the results are counter-intuitive because there is no expected activation in response to the contrast between negative and neutral distractions. These data are subject to further consideration. I am convinced that they will become the basis for generating ideas for new studies.

The third segment of the dissertation is dedicated to molecular biological measurements. Low transcriptional levels of let-7f, miR-212, miR-219, miR-126, miR-138, miR-146a, and miR-182 were found in both the patient group and the bipolar disorder and major depressive disorder groups separately compared to healthy controls. MiR-30c and miR-125b demonstrated reduced transcriptional levels in the patient group compared to healthy controls.

6. Assessment of the publications and personal contribution of the PhD student

Dr. Todeva is the first author of three articles in journals with impact factor – two reviews (in a journal of the second quartile, Q2) and one original (in a journal of the first quartile, Q1). For the most part, they are a personal merit of the PhD student.

Besides the scope of the current procedure, she is the author and co-author of 20 scientific publications, including 13 articles in journals with impact factor, and three chapters in scientific monographs indexed in Scopus. Her works have been cited over 160 times and she has a Hirsch index of 8.

I do acknowledge the following summary of contributions of this dissertation.

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 through quantitative indexing of responses/assessment of success in the studied subjects.

- An interdisciplinary approach has been applied, through which more data have been accumulated to help clarify the pathogenesis of affective disorders.

Scientific and applied

- Evidence has been generated for the role of altered connectivity of the anterior cingulate cortex and cerebellum as a possible differentiating marker in unipolar and bipolar depression.
- Pilot data were generated on the potential of the study of cerebral activity during a cognition-engaging task as a possible differentiating marker in unipolar and bipolar depression.
- Pilot data were generated for the potential possibility of establishing molecular-biological biomarkers for the diagnosis and monitoring of the therapeutic response in affective disorders.

My recommendations to Dr. Anna Todeva, which I have shared in the process of developing this doctoral thesis, are to focus on the possibility of interdisciplinary translation. In practice, this means either adapting clinical assessment methods with established psychometric characteristics to the design of a functional MRI paradigm, or vice versa – adapting a successful functional MRI paradigm to a clinical assessment test. That is legitimate way to apply valid tools in clinical practice under conditions of minimal investment of resources, such as are the conditions in psychiatry.

7, Abstract

The executive abstract covers 54 pages and fully reflects the most important highlights of the work. The abstract is prepared in accordance with the requirements and reflects the main results achieved in the dissertation.

8. Conclusion

The dissertation ***contains scientific, scientifically applied and applied results that represent an original research contribution*** and **meet the** requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its Implementation of the and the Regulations of MU - Plovdiv. The


presented materials and dissertation results **fully** comply with the specific requirements adopted in relevance to the Regulations of the Medical University – Plovdiv.

In view of the above, I confidently give my **positive assessment of** the research carried out, presented by the above-reviewed dissertation, abstract, results achieved and contributions, and **I propose to the honorable scientific jury to vote positively for granting the educational and scientific degree of 'Doctor'** to Dr. Anna Todeva-Radneva in the doctoral program in psychiatry.

I am satisfied to be involved in the preparation of this remarkable dissertation, developed under the scientific supervision of my own PhD student, now Assoc. Sevdalina Kandilarova, MD, PhD, This is how critical knowledge is embodied in a second generation of researchers in less than ten years. I believe that this is the path to the co-creation of scientific school.

· 15.08.2024 г.

Chairperson of the Scientific Jury:


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

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