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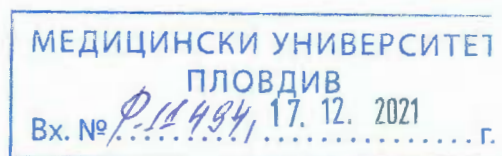
The chairman of the scientific jury,

appointed by Order № P - № P - 1882 / 22.10.2021

of the Rector of the Medical University - Plovdiv

15A V. Aprilov Blvd

4002 Plovdiv



Based on your Protocol №1 / from 03.11.2021

Attached I present: Review

In a competition for the academic position of "Associate Professor" in the scientific specialty "Psychiatry" announced for the needs of MU-Plovdiv, Department of "Psychiatry and Medical Psychology" in SG, no. 63 / 30.07.2021

Reviewer: Associate Professor Dr. Georgi Panov Panov, MD, PhD, Scientific specialty/-s Psychiatry

Institution: Asen Zlatarov University, Burgas, Faculty of Medicine, Department of Surgery, Obstetrics, and Gynecology, Nervous Diseases, Psychiatry, Physiotherapy, Rehabilitation, and ENT Diseases

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REVIEW

From Associate Professor Dr. Georgi Panov Panov, MD, PhD

FOR THE COMPETITION FOR THE ACADEMIC POSITION OF "ASSOCIATE
PROFESSOR"

IN

MU-PLOVDIV

Member of the scientific jury appointed by Order № P1882 / 22.10.2021 of the Rector of the Medical University - Plovdiv for conducting a competition for the academic position of "Associate Professor" for the needs of the Medical University - Plovdiv, Department of Psychiatry and Medical Psychology for teaching in Bulgarian and in English in the scientific specialty "Psychiatry" professional field 7.1 "Medicine", field of higher education 7. "Health and Sports", announced in SG no. 63 of 30.07.2021.

CANDIDATE: Dr. Sevdalina Sevdalinova Karaivanova-Kandilarova, MD - Chief Assistant Professor at the Department of Psychiatry and Medical Psychology, Medical University of Plovdiv.

I. Analysis of the applicant's career profile.

Dr. Kandilarova has had a master's degree in medicine since 2005, certified by a diploma from MU - Plovdiv with honours. From 2006 to 2010 she worked in Bergen, Norway consecutively as:

- 1) Research Assistant in Bergen's fMRI Group at the Department of Cognitive Neuroscience, Division of Biological and Medical Psychology at the University of Bergen under the supervision of Prof. Kenneth Hugdahl (2006 - 2007)
- 2) Resident doctor in the Department of Gerontopsychiatry at the Psychosomatic Clinic of Haukeland University Hospital (2007 - 2008)
- 3) Specializing doctor in psychiatry at the Tertnes Psychiatric Polyclinic at Haukeland University Hospital (2008 - 2010).

In 2012, following a competition, she was enrolled as a full-time doctoral student at the Department of Psychiatry and Medical Psychology at MU – Plovdiv and conducted research on "Neurophysiological markers for diagnosis and prognosis of depression", which combines quantitative electroencephalography and functional magnetic resonance imaging (fMRI). After successfully defending her dissertation thesis in 2017, Dr. Kandilarova obtained the educational and scientific degree "Doctor Philosophiae".

Since 2013 she has continued her specialization in the Clinic of Psychiatry and Medical Psychology at the University Hospital "St. George" Plc., Plovdiv, and in 2017 acquired a specialty in Psychiatry. Since February 2014, she has been appointed as assistant professor for teaching in English at the Department of Psychiatry and Medical Psychology, and since March 2018, after successful participation in a competition, she has been appointed as a chief assistant professor in the same department.

In the period 2015-2021, she was appointed as a psychiatrist at the Psychiatry Division at the Research Complex of Translational Neuroscience at MU-Plovdiv. Her main tasks in the complex included design and programming of paradigms for fMRI, extraction, and analysis of data from fMRI. She has been trained in Bergen, Norway, and Basel, Switzerland in the application of neuroimaging methods to the study of the structure and function of the brain in normal and pathological states. Two of the trainings have been accomplished thanks to received individual grants for mobility under the program of the Scholarship Fund of the European Economic Area.

Since February 2021, she has been working as a specialist in psychiatry at the Clinic of Psychiatry and Medical Psychology at the University Hospital "St. George" Plc., Plovdiv.

Summary: After successfully completing a master's degree in medicine, Dr. Kandilarova began her career development at the University of Bergen, Norway, where she became acquainted with the methods of fMRI. She continued her specialization in psychiatry at the University Hospital in Bergen, and after returning to Bulgaria she upgraded her professional and research knowledge and skills in the Department and Clinic of Psychiatry and Medical Psychology, as well as in the Research Complex of Translational Neuroscience. Due to her aspirations and perseverance, she has grown as a professional and highly qualified scientific worker.

II. General description of the materials submitted in the competition.

The materials submitted by the applicant are in full and comply with the requirements of the Act for the development of the academic staff in the Republic of Bulgaria and the Regulations of MU - Plovdiv. The materials are divided into two folders: 1) Administrative, which includes a curriculum vitae (CV), copies of diplomas, certificates of trainings in the specialty, academic positions held and study load, attestation, references of implementation of the minimum national scientometric criteria, certificates and other documents evidencing various academic activities and skills; 2) Folder with scientific work, where the distribution is made according to the indicators of the minimum national requirements. The jury was presented with 29 scientific works, including - 1) full-text publications in foreign journals with an impact factor - 20; 2) in foreign referenced journals without an impact factor - 2; 3) in national journals and

scientific collections - 2; 4) summaries in foreign journals with an impact factor - 3; 5) summary in foreign journals/collections without an impact factor - 1 and a summary of participation in a national forum - 1.

Evidence for participation in the author's team of 4 textbooks for medical students in Bulgarian and English in the subjects Psychiatry and Medical Psychology are respectively presented.

In the competition, the applicant submitted 50 citations of her scientific work in referenced journals, 49 of which were in journals with IF mostly between 3 and 6, reaching 13,382.

Dr. Kandilarova has taken part in 2 international, 3 national, and 4 university projects, for which she presents detailed evidence.

III. Evaluation of the applicant's scientific works for the overall academic development.

General characteristics of the scientific production and publishing activity:

For her participation in the competition, Dr. Kandilarova presented 24 full-text scientific publications, 5 scientific reports, and 4 textbooks. In scientific journals with an impact factor, 20 texts were published (over 80% of the total number), and in referenced journals without IF and in non-indexed national journals without IF, respectively, 2 articles each. The applicant is the first or the second author in most of the scientific papers, which describe mostly original research. The review publications are 4 in number. In a large percentage of cases, she is a co-author with researchers from Norway and Switzerland.

The presented works can be grouped in the following main directions:

Unconventional functional MRI

In this direction, is the largest part of the research of the applicant, including an abstract from the dissertation, 7 original and 2 review articles, as well as one report at an international forum. The defended doctoral dissertation presents the results of a study of patients with depression and healthy controls by fMRI in performing a task that includes a motor response to visually presented stimuli from the von Zerssen depression questionnaire (marked as diagnostically specific), contrasted against diagnostically neutral ones. The study aims to determine the sensitivity of the method of translational cross-validation of clinical-psychological scales and fMRI (its ability to distinguish norm from pathology), as evidenced by statistically significant differences in brain activations in patients and controls.

In the course of this work, an upgrade of the paradigm has been developed that includes stimuli from the von Zerssen's paranoia questionnaire. It is used in patients with

schizophrenia and depression and the results show the specificity of the translation method, i.e. its ability to distinguish individual mental disorders. Besides the classical methods for statistical analysis such as Student's t-test and ANOVA, some of the publications also use machine learning based methods. Multimodal data from 3 sequences were used - structural and functional MRI at rest and during performing tasks on which multivariate analysis was applied, in contrast to the classical univariate methods. As a result, evidence has been found of the possibility of successful convergent cross-validation between clinical-psychological assessment scales and fMRI images when applied together. Specific regions of activation and brain signatures have been identified that distinguish paranoid patients from those with the depressive syndrome. Results have been presented regarding the contribution of the individual image modalities, respectively structure, function at rest, and function during performing a task to the differential diagnosis of schizophrenia and affective disorders. This scientific research has contributed to the development of the methods of translational neuroscience and their application in psychiatry.

Conventional task related fMRI

In collaboration with neurologists, studies have been conducted on patients with multiple sclerosis and healthy controls by applying a paradigm programmed by Dr. Kandilarova to study cognitive functions. The results have shown that lower performance during the task correlates with greater activation in areas related to working memory, attention, and emotional processes during fMRI.

Functional MRI at rest

A significant emphasis in the applicant's research work is the research of brain connectivity measured by fMRI at rest using the method of spectral dynamic causal modeling. In such a study, three groups of patients with schizophrenia, bipolar and unipolar depression have been scanned. Individual connections have been identified representing potential differential diagnostic markers with an overall accuracy of up to 75%. Similar studies contribute to the identification of connectivity disorders in major mental disorders with great social significance.

In another study of patients with schizophrenia and patients with depression, data from fMRI at rest and from the implementation of an unconventional paradigm for translational validation of clinical psychological scales have been combined. Aberrant connectivity has been found between the anterior insula and the medial frontal gyrus, showing a significant difference between the two groups with inhibitory connection, found only in patients with schizophrenia.

The results of both studies could suggest that the connectivity between the dorsolateral prefrontal cortex (DLPFC) and the anterior insula can be interpreted as evidence of an

aberrant network that leads to behavioral abnormalities that depend on the direction of impact. Decreased effective connectivity from the anterior insula to the DLPFC manifests as depressive symptoms, and the inhibitory effect of DLPFC to the anterior insula is reflected in the paranoid symptoms of schizophrenia. These conclusions represent a significant contribution to the hypotheses of disconnectivity as a major pathophysiological mechanism in psychotic and affective disorders.

✓Scientific activity – dissemination and application of the applicant’s scientific and practical achievements among the scientific community;

The applicant speaks at international and national conferences with reports summaries of which are published in journals with IF. Dr. Kandilarova’s applied and practical contribution is the developed original paradigms for fMRI during performing tasks that are used by researchers in the Complex for Translational Neuroscience.

✓Participation in project implementation:

She has participated in 2 international projects with the University of Bergen, Norway, and the University of Lausanne, Switzerland, and she is a leading researcher in both. The topics of the projects are related to the study of hallucinations through fMRI at rest and the testing of an innovative platform for the automatic analysis of MRI data. The successful work on these topics has resulted in several joint publications.

Dr. Kandilarova also participates in 3 national projects, one of which with international participation and focus on increasing the researchers’ capacity at MU – Plovdiv through the transfer of knowledge and skills from highly qualified European centers. Participations in 4 intra-university projects have been presented in wide collaboration with researchers from the Departments of Microbiology and Immunology, Pathological Physiology, Biology, which collaboration has been evidenced by joint publications.

✓Scientific and creative achievements (scientific authority);

Dr. Kandilarova demonstrates a high citation index (Hirsch Index 7 in Scopus), which shows her scientific authority. She is a reviewer of prestigious journals with impact factor such as the “Journal of Affective Disorders” and “Acta Radiologica”, and has produced 8 reviews for various national and foreign journals.

IV. Evaluation of the monograph or equivalent publications submitted for participation in the competition for "ASSOCIATE PROFESSOR".

Instead of a monograph, 10 original publications are presented in refereed editions with IF, joint in the following areas:

fMRI at rest

Dr. Kandilarova has used the method of effective connectivity to establish not only the connection between different regions of interest but also their direction and strength. Through spectral dynamic causal modeling, it has determined the inhibitory or excitatory influence of one brain area over another. In her study of patients with depression and healthy controls, she has found that patients had a significantly reduced strength of the connectivity from the anterior insula to the dorsolateral prefrontal cortex and has demonstrated a connection between the amygdala and the anterior insula that was missing in the healthy controls. A significant correlation between the severity of depression and the connectivity of the hippocampal node has also been found. This research has produced evidence for the role of the anterior insula in the pathophysiological mechanisms of depression and it has been shown in positive citations, which are over 20 for a period of 2 years. All of them are in journals with IF up to 13,382.

Structural MRI in depression

A study using the quantitative method of voxel-based morphometry applied to data from patients with depression and healthy controls has been reported. Patients have demonstrated significant reduction in the volume of gray matter in certain regions of the frontal and temporal lobes. The results have been subsequently used in a meta-analysis comparing patients with depression, anxiety disorders, and post-traumatic stress disorder. Structural correlates specific to the particular disorders have been found, which enriches our understanding of the neurobiological mechanisms of these common mental disorders.

Unconventional task related fMRI - classical univariate and multivariate analyzes

As mentioned above, Dr. Kandilarova has been involved in the development of an innovative research model that combines routinely used scales for clinical psychological evaluation with simultaneous use of fMRI to identify "bridges" of translation between neuroimaging markers and clinical psychological scales. The results of this study prove the specificity of the method, i.e. the ability to distinguish different psychopathological constructs.

Along with the classical univariate analyzes, several publications have used multivariate analysis based on machine learning when using multimodal data from structural and functional MRI at rest and during task performance. Thus, convincing data have been generated for the successful convergent cross-validation between clinical-psychological assessment scales and fMRI images with the establishment of specific activations and brain signatures specific to different patients' groups (with paranoid and depressive syndrome respectively). Determining the contribution of the various modalities

(structure, function at rest and in task) has a particularly high scientific and practical value to the differential diagnosis of schizophrenia and affective disorders.

Conventional task related fMRI

Dr. Kandilarova has been developing another original block paradigm with affectively charged stimuli from the International Affective Pictures System (IAPS). The application of fMRI in patients with depression and healthy controls along with structural MRI has resulted with evidence of the advantage of multivariate analysis methods in multimodal data from structural and task related fMRI compared to classical univariate methods.

V. Reflection (citation) of the candidate's publications in the national and foreign literature (publication image).

Proof of the qualities of Dr. Kandilarova's scientific publications are their high international impact, reflected in the presented positive citations, which are 50 in total, 49 of them are in journals with impact factor, most often between 3 and 6. As it was mentioned above, the publication establishing impaired effective connectivity of the anterior insula in depression has been cited in an article in IF 13.382. The candidate's Hirsch index is 7 in the Scopus database.

VI. Complex, quality assessment of methodological and teaching activities, incl. scientific guidance of students, doctoral students, postgraduates.

Dr. Kandilarova has over seven years of teaching experience as an Assistant Professor at the Department of Psychiatry and Medical Psychology at MU - Plovdiv. According to the academic report for the last 3 academic years, Dr. Kandilarova's study load is much above the norm (on average over 200%). Throughout her teaching career, she has conducted practical trainings for students of medicine and dentistry in English and has participated in Erasmus program. Since 2016, she has been contributing to the training of general practitioners. Since 2017, she has systematically trained students, doctoral students, and lecturers in the methods for paradigm design and data processing by fMRI. In 2020, she organized and conducted specialized theoretical and practical training for graduate and doctoral students in the methods of fMRI.

Dr. Kandilarova has successfully shared her experience with potential future researchers, as evidenced by the attached list of over 15 publications and projects involving graduate and doctoral students.

VII. Critical remarks and recommendations.

None

VIII. A general assessment of the applicant's compliance with the minimum national requirements under Article 2b, paragraph 2 and 3, respectively to the requirements under Article 2b, paragraph 5 of LDASRB, and the specific requirements of MU - Plovdiv in areas and for units with/without clinical activity, defined in the Regulations for academic development at the Medical University – Plovdiv:

As it can be seen from the attached table, the applicant's performance is several times higher than the minimum requirements.

Group of indicators	Minimum requirements	Real applicant's indicators
Group A	50	50
Group B	100	103.37
Group C	200	244.14
Group D	100	750
Group E	60	196.7
Group F	300	677.25
Total	810	2021.46

IX. Conclusion

Dr. Kandilarova has achieved original research results with both practical and scientific significance. She has the authority of an established professional, lecturer, and researcher with international recognition. Her overall scientific and teaching activity meets the mandatory and specific conditions and scientometric criteria set out in the LDASRB, the Regulations for its implementation, and the Regulations of MU-Plovdiv for the academic position of "Associate Professor".

Based on this, I give a positive review for the award of the academic position of "Associate Professor", in the scientific specialty Psychiatry, in the Department of Psychiatry and Medical Psychology at MU - Plovdiv to Dr. Sevdalina Sevdalinova Karaivanova-Kandilarova, MD.

07.12.2021

Associate Professor Georgi Panov, MD, PhD