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Review

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This is a critical review of the dissertation “Translation cross-validation of neuroimaging and molecular biomarkers in the differential diagnosis of unipolar and bipolar depression” by Dr. Anna Aleksandrova Todeva-Radneva, for the acquisition of educational and scientific degree Doctor of Philosophy in the field of Medicine (Psychiatry).

In preparation of this report, I have reviewed the above thesis, written in Bulgarian, and the Abstract of the thesis, provided in both Bulgarian and English. The thesis

is written on 122 pages and illustrated with 11 tables and 16 figures and has cited 246 references. The thesis was approved and directed for defense by an extended departmental council of the Department of Psychiatry and Medical Psychology at the medical University of Plovdiv.

The thesis starts with an introduction, focusing on the importance of clear diagnostic criteria for mental disorders, which are currently mainly based on phenomenology. Diagnosing mental disorders based on nonspecific clusters of symptoms is also responsible for the high level of comorbidities currently encountered when using the diagnostic manuals. The lack of biological markers as basis of the diagnosis based on new findings in neurosciences is emphasized. In the absence of an appropriate diagnosis, it is not surprising that the treatment methods used are not necessarily effective in treating the disorders and preventing future episodes. The importance of diagnosing and treating mental illness becomes a high priority, as according to the World Health Organization are increasing and the frequency of both major depressive disorder and bipolar disorder and affect over 300 million people worldwide.

Traditionally bipolar disorder and major depressive disorder have been seen as different categories of mental disorders although more recently they seem to be conceptualized as continuum. The importance of developing new diagnostic criteria to differentiate between depressive episodes in the context of bipolar disorder and major depressive disorder is emphasized amply.

A brief historical review of psychiatric classification starting from the idea of unitary psychosis developed by Griesinger, and E. Krepelin's nosologic approach

for psychiatric classification, is used as a starting point to position the goals and task of the work later on. A detailed review of the current literature of using MRI and fMRI is provided and the specific focus is on structural and anatomical findings in different areas of the brain, including a reduction of gray matter in the cortex and changes in the deeper brain structures such as limbic system, anterior cingulate cortex, thalamus, hippocampus etc. The literature review also focuses on the role of genetic and epigenetic factors in the pathophysiology of the affective disorders. There have been renewed focus on noncoding and micro RNAs and depressive disorders, specifically being used to measure therapeutic response.

The detailed literature review allows the formulation of specific goals and tasks the main goal for the thesis is the investigation of potential differential diagnosis biomarkers from both imaging and molecular aspects. The following tasks have been formulated: assessment and comparative analysis of the functional connectivity at rest in both patients and healthy controls; evaluation of differences in functional MRI during cognitive task in patients with major depressive disorder or bipolar disorder; evaluation of the differential expression of preselected noncoding RNA and microRNA linked to disturbances of sleep in major depressive disorder and bipolar disorder (in collaboration with Department of Pathophysiology). This research applies new statistical methods for analysis of already collected imaging data, and implementing the new paradigm of fMRI in an independent cohort.

Inclusion criteria were age between 18 and 65 with established DSM-5 diagnosis of major depressive disorder or bipolar disorder with moderate or severe depressive episode with MADRS of over 20 and YMRS below 3. People with

high suicidal risk were excluded and for healthy controls, any history of past psychiatric disorders were exclusionary as well.

A total of 115 participants including 45 healthy controls; 35 patients with depressive episodes and major depressive disorder, and 35 patient's with major depressive episode in bipolar disorder. Twelve participants were excluded because of artifacts resulting in final sample of 103 participants (43 healthy controls 35 major depressive episode and depression, 25 and bipolar depression).

The second component recruited 96 participants of Home 50 healthy controls and 46 patient's with depressive episode with either major depressive disorder or bipolar disorder after excluding 18 participants for a variety of different reasons the final group consisted of 78 participants of home and 40 were healthy controls 23 were with major depressive disorder and 15 with bipolar depression

The research project included significant experiments, evaluation and analysis, which are well described in the text, and the results are presented clearly in both text and figures and tables. There are some significant findings in both imaging and structural anatomical but also functional MRI. The use of peripheral biomarkers is also well documented.

The discussion section is very comprehensive and compares the findings with the literature review and results of this work connecting logically and thoughtfully.

The conclusions of the presented work are valid and reflect the experimental and analytical work of the project. They are well summarized in the thesis, but briefly

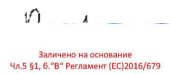
the alterations in functional connectivity are found in patients with depression but not in healthy controls are pointers for many of the underlying morbid processes in both unipolar and bipolar depression. Furthermore, some specific differences might be used in the future for differentiating of unipolar and bipolar depressions. The examination and analysis of micro RNAs can also help with the understanding of some non-specific symptoms, common in both disorders, but also across other mental disorders.

There are significant theoretical and methodological contributions, such as developing a new paradigm for exploring cognitive functions with emotional distractors, and using an interdisciplinary translation approach to generate additional data to help elucidate the etiology and pathogenesis of the affective disorders. Other contributions to the field included demonstrating the possibility of using the altered conductivity between the anterior cingulate cortex and cerebellar cruri as a potential differentiating marker in unipolar and bipolar depression. Some of the collected pilot data could be useful for future examination of cerebellar activity during cognitive tasks, in order to help differentiating unipolar from bipolar disorder. Furthermore, some pilot data was generated from potential establishment of molecular biological biomarkers for the diagnosis and monitoring of treatment response in mood disorders.

Dr. Todeva-Radneva has presented parts of this research at several national and international meetings, and has published three peer-reviewed articles as a first author.

In summary, the presented thesis and abstracts fulfill the requirement for conferring the title of doctoral philosophy and recommend the honorable jury to endorse Dr Todeva for the degree of PhD in psychiatry.

Sincerely,



Заличено на основание
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