



From pathogenesis of stress-related mental disorders to treatment: beyond the brain

Xiaoxing Liu¹ · Lin Lu^{1,2,3}

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Stress pervades every aspect of life in contemporary society, stemming from work, daily routines, and unexpected events. Consequently, the prevalence of stress-related mental disorders, such as anxiety, depression, and posttraumatic stress disorder (PTSD), have markedly increased [1]. These conditions impose a significant health burden by affecting not only mental well-being but also physical health, garnering escalating attention from both the general public and medical professionals alike. Some studies have focused on elucidating neural underpinnings of these disorders. Recent evidence has shed light on the role of other systems [2]. Although precise causal relationships remain unclear, research in this field has provided novel insights into the pathogenesis of stress-related mental disorders and potential therapeutic approaches. This issue of *European Archives of Psychiatry and Clinical Neuroscience* features multiple articles that delve into anxiety disorders, PTSD, bipolar disorder, and depression, encompassing risk factors, biomarker identification, and treatment strategies.

Three studies were conducted to investigate anxiety disorders and PTSD. Hsu et al. [3] examined the impact of PTSD on autoimmune diseases through a nationwide cohort study with a 10-year follow-up period. The study recruited 5,273 Asian individuals with PTSD and 21,092 healthy controls. Compared with the control group, patients with PTSD had

a higher risk of developing various autoimmune disorders, including Sjogren's syndrome, lupus, and thyroiditis (i.e., the three diseases that posed the highest risk). A greater severity of PTSD symptoms was associated with a higher risk of developing these autoimmune disorders. These findings suggest the importance of considering autoimmune diseases in the prognosis of individuals with PTSD.

Five studies investigated various aspects of bipolar disorder, including its neural substrates, potential biomarkers, and risk factors. Karademir et al. [4] examined diagnostic biomarkers relative to steroid hormones for bipolar disorder. They recruited 41 euthymic male patients with bipolar disorder and 40 healthy controls, and found lower serum levels of allopregnanolone and progesterone in patients compared with controls. Notably, serum allopregnanolone levels had a stronger association with the development of bipolar disorder, which negatively correlated with disease duration and positively correlated with performance on neurocognitive tests. This study suggests that serum allopregnanolone could serve as a potential biomarker for identifying and managing disease symptoms, particularly cognitive functions, in individuals with bipolar disorder. In addition to cognitive deficits in bipolar disorder, motor activity dysregulation is also a prevalent symptom. A longitudinal study by Marten et al. [5] identified impairments in performance on finger tapping tasks in individuals with bipolar disorder compared with healthy controls. They also found that these motor deficits were positively associated with anti-correlated functional connectivity between the posterior cingulate cortex and supplementary motor area. These findings demonstrate that individuals with bipolar disorder experience deficits in motor activity and lower posterior cingulate cortex–supplementary motor area connectivity.

The current issue of the journal also includes 12 studies of depression and one study of non-suicidal self-injury (NSSI) in adolescents. Chen et al. [6] employed a cross-sectional design to investigate the association between glucose disturbances and major depressive disorder (MDD). They

✉ Lin Lu
linlu@bjmu.edu.cn

¹ Peking University Sixth Hospital, Peking University Institute of Mental Health, NHC Key Laboratory of Mental Health (Peking University), National Clinical Research Center for Mental Disorders (Peking University Sixth Hospital), 51 Huayuanbei Road, Haidian District, Beijing 100191, China

² National Institute On Drug Dependence and Beijing Key Laboratory of Drug Dependence Research, Peking University, Beijing 100191, China

³ Research Unit of Diagnosis and Treatment of Mood Cognitive Disorders, Chinese Academy of Medical Sciences, Beijing, 100730, China

reported a prevalence of 13.6% for glucose disturbances in 1,718 drug-naive MDD patients who experienced their first episode. Comorbid glucose disturbances also showed a robust correlation with severe symptoms in these MDD patients, encompassing depression, anxiety, psychotic symptoms, Body Mass Index, and suicide attempts. This study suggests that glucose disturbances should be considered a significant comorbidity of MDD, particularly during the acute early phase. It is also imperative to closely monitor disease progression and overall health in MDD patients with disruptions of glucose metabolism. Furthermore, metabolic syndrome (MetS) and subclinical hypothyroidism (SCH) are two other prevalent comorbidities in individuals with MDD. Peng et al., [7] investigated relationships among MetS, SCH, and MDD in 1,706 drug-naive MDD patients during the acute early phase of the illness. The prevalence of MetS was 34.5%, and the prevalence of SCH was 61% among these subjects. Moreover, MetS and SCH showed a potentially synergistic relationship, in which SCH increased the risk of developing MetS, and MetS was positively associated with disease symptoms only in individuals with coexisting SCH. These studies underscore the importance of the early management of comorbidities among individuals who are diagnosed with MDD to alleviate disease burden and promote recovery. Another study by Zhou et al. [8] found disturbances of brain–heart synchronization in MDD patients compared with healthy controls, providing new insights into the pathogenesis of MDD. The crucial role of the brain–heart interaction was also identified in patients with NSSI. Sigrist et al. [9] reported aberrant cardiac autonomic activity in female adolescents with NSSI, characterized by dysregulated rhythm-adjusted levels, amplitudes, and acrophase shifts in heart rate and heart rate variability. This study highlights deficits in cardiac activity within the context of NSSI, which may be associated with impairments in inhibitory control and decision-making.

This issue of the journal also includes studies of the safety and efficacy of treatment strategies. Grosse et al. [10] explored the therapeutic effect of combining an individual pedometer intervention (PI) with an activity diary and inpatient treatment on depression, but no statistically significant difference was found between patients who underwent the PI + TAU intervention and those who received only TAU. Future research should employ more reliable measurement equipment.

Numerous studies in the field of stress-related mental disorders have increasingly emphasized the significance of extra-neural factors and their potential to redefine these mental disorders. Moreover, adopting novel perspectives beyond the nervous system may contribute to the identification of new biomarkers and facilitate the development of safe, effective, and convenient therapies.

Declarations

Conflict of interest Lin Lu is Editor at European Archives of Psychiatry and Clinical Neuroscience. The authors declare no further competing interest.

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