Exploration of Neuroscience

Open Exploration

Open Access Editorial

Editorial: novel therapeutic approaches for the treatment of depression

Ayan Mohamud Yusuf, Dirk M. Hermann*

Department of Neurology, University Hospital Essen, University of Duisburg-Essen, 45147 Essen, Germany

***Correspondence:** Dirk M. Hermann, Department of Neurology, University Hospital Essen, University of Duisburg-Essen, Hufelandstr. 55, 45147 Essen, Germany. dirk.hermann@uk-essen.de

Academic Editor: Dirk M. Hermann, University of Duisburg-Essen, Germany

Received: September 7, 2025 **Accepted:** September 8, 2025 **Published:** September 16, 2025

Cite this article: Mohamud Yusuf A, Hermann DM. Editorial: novel therapeutic approaches for the treatment of depression. Explor Neurosci. 2025;4:1006110. https://doi.org/10.37349/en.2025.1006110

Keywords

depression, treatment refractory depression, antidepressants, electroconvulsive treatment, transcranial magnetic stimulation, ketamine

Depression is one of the most common psychiatric disorders and a leading cause of disability worldwide [1]. Despite decades of research, the molecular pathogenesis of depression and the precise modes of action of antidepressants remain only partly understood [2]. While classical treatments have largely targeted monoaminergic neurotransmission, many patients fail to respond, leaving a significant proportion with treatment-resistant depression (TRD), which is defined as the lack of clinical improvement after at least two antidepressant treatments, each administered at an adequate dose and duration with confirmed adherence [3]. This clinical challenge has stimulated interest in novel therapeutic avenues such as electroconvulsive therapy (ECT), transcranial magnetic stimulation, and ketamine, as well as in adjunctive strategies that address immune, endocrine, and metabolic dysregulation. The articles included in this Special Issue illustrate how diverse perspectives, ranging from biological and immunological factors to psychological frameworks, can enhance our understanding of depression and thereby enable the development of more effective treatments.

This Special Issue published eight articles, which explore multiple aspects of depression, including the role of inflammatory processes in the brain. Goischke [4] emphasizes that multiple sclerosis and depression share common immune and neurological mechanisms that are closely linked to insufficient vitamin D levels. As such, both diseases are associated with an imbalance of proinflammatory and anti-inflammatory cytokines, elevated serum neurofilament light chains, disruption of the blood-brain barrier, dysfunction of microglia, disturbances of the gut microbiome, and hyperactivity of the hypothalamic-pituitary-adrenal axis. Goischke [4] further reports that vitamin D supplementation may serve as an immunomodulatory and neuroprotective intervention. In a complementary manner, Vollbracht and Werner [5] emphasize that oxidative stress plays a key role in the pathophysiology of depression, impairing neuronal metabolism and reducing response rates to antidepressants. Vitamin C, a potent antioxidant and anti-inflammatory immunomodulator, is closely linked to these processes, and a suboptimal vitamin C status is associated with

increased depressive symptoms and cognitive impairment. As Vollbracht and Werner [5] point out, vitamin C deficiency is more common than generally recognized, particularly in patients with poor nutrition or mental disorders, and may contribute to what has been termed neuropsychiatric scurvy. Although evidence for the benefits of pharmacological vitamin C supplementation is still limited, its role in supporting neuronal function, neurotransmitter synthesis, and reducing oxidative stress suggests that addressing its deficiency could be an important element in depression management. Together with Goischke's discussion [4] of immune and inflammatory pathways, these two contributions demonstrate that depression cannot be fully understood in isolation from systemic, immunological, and oxidative processes.

In line with this Special Issue's focus on advancing the understanding of depression, Jagtiani's review [6] examines emerging therapeutic approaches that extend beyond traditional antidepressants, including pharmacologic agents, neuromodulation techniques, and lifestyle-based interventions. Jagtiani [6] highlights novel pharmacologic strategies such as ketamine and esketamine, which act on the glutamatergic system to produce rapid antidepressant effects. In patients with depression, elevated levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) are commonly observed. These cytokines can promote neuroinflammation and interfere with normal neuroregulatory processes, playing a key role in the onset and persistence of depressive symptoms. Hence, anti-inflammatory agents are also discussed by Jagtiani [6] as potential treatments for depression. Further, GABA modulators, such as brexanolone and psychedelic-assisted therapies that enhance neuroplasticity through serotonin receptor modulation, are presented as promising interventions. Additionally, Jagtiani [6] explores the role of gut-brain axis interventions, including probiotics, prebiotics, and anti-inflammatory diets in alleviating depressive symptoms through modulation of neurotransmitter synthesis and inflammation. Jagtiani [6] further discusses the utility of non-pharmacologic treatments. Ketamine-assisted ECT may accelerate early antidepressant effects, while repetitive transcranial magnetic stimulation (rTMS) offers a non-invasive, FDA-approved approach for TRD, demonstrating efficacy in adults and the elderly, with emerging evidence for adolescents. Further, magnetic seizure therapy (MST) provides targeted seizure induction with fewer cognitive side effects than traditional ECT. Transcranial direct current stimulation (tDCS) modulates cortical activity and shows modest antidepressant effects with minimal side effects. Invasive techniques, such as deep brain stimulation (DBS) and vagus nerve stimulation (VNS), modulate neural circuits involved in mood regulation and have shown benefits for select patients, though they require careful monitoring due to higher risks. Overall, Jagtiani [6] illustrates that these emerging treatments offer promising alternatives to conventional antidepressants by targeting novel mechanisms implicated in depression, including glutamatergic and GABAergic signaling, inflammation, gut-brain interactions, and neural network function. While intranasal esketamine has gained notable clinical traction, many of these approaches remain limited to specialized or investigational settings, highlighting the need for further research to optimize their efficacy, safety, and accessibility.

Reflecting the Special Issue's emphasis on novel therapeutic strategies, Norman's review article [7] examines psilocybin-assisted psychotherapy (PAP) as a treatment for TRD, highlighting its rapid antidepressant effects, mechanisms of action, and clinical potential. Psilocybin, a naturally occurring hallucinogen found in certain mushrooms, is rapidly converted in the body to its active form, psilocin. Its antidepressant effects are largely mediated through agonism at 5HT2A receptors, which trigger downstream signaling, promote neuroplasticity, and increase brain-derived neurotrophic factor (BDNF). Clinical studies show that a single dose of psilocybin combined with psychological support can produce rapid, clinically significant reductions in depressive symptoms, often sustained for several weeks to months. Psilocybin is generally well-tolerated, with mild to moderate side effects such as headache, nausea, fatigue, and transient blood pressure changes. Serious adverse events are rare, and the risk of lethality is extremely low. Though hallucinogen persisting perception disorder and increases in suicidal ideation are reported occasionally, mainly in vulnerable individuals. In this article, Norman [7] also highlights ongoing challenges, including standardizing psychological support, determining optimal dosing of psilocybin, managing placebo effects, and identifying patients most likely to benefit. Regulatory changes, such as the reclassification of psilocybin for TRD by Australia's regulatory authority for therapeutic goods, signal a shift

toward wider therapeutic use under controlled conditions. Overall, the article concludes that PAP offers a promising rapid-acting alternative for patients with TRD, but larger, controlled trials are needed to confirm efficacy, optimize treatment protocols, and ensure long-term safety.

The article by Ruiz-Marquez [8] explores the role of executive cognitive functions, including planning, decision-making, working memory, attention, inhibitory control, and mental flexibility, and points out that executive cognitive deficits significantly influence remission and recurrence of depression. To understand the neurocognitive mechanisms underlying these executive processes, Ruiz-Marquez [8] conducted a literature search and summarized the key findings of experiments in which electrophysiological techniques were used. Ruiz-Marquez [8] points out that depression is associated with alterations in several brain components linked to cognitive function. For example, the P3 component shows reduced amplitude and delayed timing, reflecting deficits in attention, working memory, and decision-making. Early sensory processing components, N1 (an early negative wave associated with attention and sensory discrimination) and P2 (a positive wave following N1 linked to pre-attentive processing), are also affected. Changes in loudness dependence of auditory evoked potentials (LDAEP), which measure how N1/P2 responses vary with sound intensity and reflect serotonin function, suggest deficits in inhibitory control and impulsivity in depression. Additionally, depression alters brain responses related to error and feedback processing, including error-related negativity (ERN), error positivity (Pe), and correct response negativity (CRN), indicating difficulties with error awareness, cognitive control, and adapting behavior based on feedback. Finally, depression is linked with poorer performance on tasks measuring executive function, often resulting in both perseverative and non-perseverative errors, which relate to disruptions in frontal-striatal brain networks. In conclusion, Ruiz-Marquez's review [8] highlights multiple neurocognitive mechanisms underlying executive deficits in depression and emphasizes that these deficits contribute to challenges in attention, decision-making, inhibitory control, and mental flexibility. Ruiz-Marquez [8] emphasizes that further research is needed to resolve inconsistencies related to depression heterogeneity, comorbidities, demographic differences, and experimental methods. Following the review of executive cognitive deficits, Ruiz-Marquez [9] introduces a trial protocol aimed at evaluating how exergames may enhance cognitive and psychomotor functions in individuals with depression. The protocol outlines participant selection criteria, including adults aged 20–60 with depression, while excluding those with certain comorbidities or cognitive impairments. The study employs a three-arm, double-blind, parallel-group design with pre-intervention, post-intervention, and three-month follow-up assessments. Participants are randomly assigned to one of three groups: an exergame intervention combining cognitive and physical stimulation, an active control group using cognitive video games, or a passive control group on a wait-list. Executive functions are assessed behaviorally using the Wisconsin Card Sorting Test, and neural activity is measured through event-related potentials. The protocol also provides detailed procedures for EEG recording, stimulus presentation, and artifact handling, as well as for data analysis. It also includes methods to control for placebo effects, motivation, and engagement. Overall, this work establishes a rigorous methodological framework for exploring how exergames may improve cognitive and neural functions of patients suffering from depression.

Highlighting innovative strategies to overcome barriers to care, Posmontier et al. [10] describe the use of the PRECEDE-PROCEED model, a comprehensive planning and theoretical framework, to guide the design and development of MommaConnect, a digital healthcare platform for women experiencing postpartum depression (PPD). PPD affects roughly one in eight mothers and negatively impacts both maternal functioning and infant development, but access to specialized, evidence-based treatment is limited due to barriers such as stigma, socioeconomic factors, and geographic constraints. The eight-step PRECEDE-PROCEED model was applied iteratively to assess social, epidemiological, behavioral, environmental, educational, ecological, and organizational factors affecting PPD care. These data guided the design of MommaConnect, which includes features such as remote psychotherapy, psychoeducation, mood tracking, mother-infant interaction support, and clinician communication tools. Future work will involve feasibility testing, randomized controlled trials, and evaluation of cost-effectiveness. The study demonstrates that the PRECEDE-PROCEED model is a valuable framework for developing digital interventions that address barriers to mental health care and improve outcomes for mothers and infants.

Afshari's article [11] complements this Special Issue by extending the focus from unipolar depression to bipolar disorder (BD), which also features recurrent depressive episodes. Current treatments for BD, a condition shaped by genetic, neurobiological, neuropsychological, and psychological factors, include medication and several psychotherapies such as cognitive behavioral therapy (CBT), interpersonal and social rhythm therapy (IPSRT), dialectical behavior therapy (DBT), family-focused therapy (FFT), and mindfulness-based cognitive therapy (MBCT). Each approach provides partial benefits but does not fully address the disorder's complexity. To overcome this, Afshari [11] proposes an integrated model centered on individualized, multi-component therapy. This approach begins with a comprehensive assessment of the patient's cognitive, emotional, behavioral, and personality functioning, then modifies the treatment approach by combining techniques from different evidence-based therapies. For example, CBT strategies may be used to manage negative thinking, DBT skills to improve emotion regulation, IPSRT to stabilize daily rhythms, FFT to strengthen family support, and MBCT to build mindfulness and prevent relapse. By merging these methods, the model aims to target both depressive and manic symptoms, enhance coping skills, and adapt flexibly to each patient's unique needs.

Together, the contributions in this Special Issue demonstrate the multifaceted etiology of depression and highlight the need for innovative and integrative approaches for its treatment. From biological and immunological perspectives, including the roles of inflammation, oxidative stress, and vitamin deficiencies, to emerging pharmacologic and neuromodulatory interventions, the articles presented in this Special Issue expand our knowledge of the mechanisms underlying depressive symptoms. Complementary psychological and neurocognitive approaches, as well as digital and lifestyle-based interventions, emphasize the importance of addressing cognitive deficits, executive functioning, and accessibility barriers. Successful and comprehensive management of depressive disorders therefore depends on combining molecular, neurobiological, psychological, and practical strategies to achieve more targeted and effective interventions.

Abbreviations

BD: bipolar disorder

CBT: cognitive behavioral therapy

DBT: dialectical behavior therapy

ECT: electroconvulsive therapy

FFT: family-focused therapy

IPSRT: interpersonal and social rhythm therapy

MBCT: mindfulness-based cognitive therapy

PAP: psilocybin-assisted psychotherapy

PPD: postpartum depression

TRD: treatment-resistant depression

Declarations

Acknowledgments

We thank all authors for their contributions to this Special Issue.

Author contributions

DMH and AMY: Conceptualization, Writing—original draft, Writing—review & editing. Both of the authors read and approved the submitted version.

Conflicts of interest

Dirk M. Hermann is the Editor-in-Chief and Guest Editor of *Exploration of Neuroscience* (*EN*). Ayan Mohamud Yusuf is the Guest Editor of *EN*. Ayan Mohamud Yusuf was not involved in the decision-making or the review process of this manuscript.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

Publisher's note

Open Exploration maintains a neutral stance on jurisdictional claims in published institutional affiliations and maps. All opinions expressed in this article are the personal views of the author(s) and do not represent the stance of the editorial team or the publisher.

References

1. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9:137–50. [DOI] [PubMed] [PMC]
2. Cui L, Li S, Wang S, Wu X, Liu Y, Yu W, et al. Major depressive disorder: hypothesis, mechanism, prevention and treatment. Signal Transduct Target Ther. 2024;9:30. [DOI] [PubMed] [PMC]
3. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry. 2023;22:394–412. [DOI] [PubMed] [PMC]
4. Goischke HK. Multiple sclerosis with comorbidity depression and its association with vitamin D deficiency in a narrative review of the current literature. Explor Neurosci. 2023;2:160–92. [DOI]
5. Vollbracht C, Werner M. The role of inflammation and oxidative stress in the pathophysiology of depressions: time to consider vitamin C deficiency. Explor Neurosci. 2024;3:287–94. [DOI]
6. Jagtiani A. Novel treatments of depression: bridging the gap in current therapeutic approaches. Explor Neurosci. 2024;3:272–86. [DOI]
7. Norman TR. The psychedelic renaissance: psilocybin, a breakthrough for treatment resistant depression? Explor Neurosci. 2025;4:1006105. [DOI]
8. Ruiz-Marquez E. Neurophysiology of executive cognitive functions under depression. Explor Neurosci. 2025;4:100696. [DOI]

9. Ruiz-Marquez E. Protocol for measuring the benefits of exergames on executive functions under depression through a randomized multi-arm controlled experiment. Explor Neurosci. 2024;3:564–83. [DOI]
10. Posmontier B, Horowitz JA, Geller PA, Elgohail M, McDonough M, Alvares K, et al. Applying the PRECEDE-PROCEED model to develop MommaConnect: a digital healthcare platform for addressing postpartum depression and improving infant well-being. Explor Neurosci. 2024;3:309–20. [DOI] [PubMed] [PMC]
11. Afshari B. Psychology of bipolar depression: revisiting past and present researches, prospects ahead, and moving toward future directions. Explor Neurosci. 2023;2:331–49. [DOI]