Proceedings of ICMMGH 2026 Symposium: Cell and Molecular Biology: Understanding Immune Cell Functions
DOI: 10.54254/2753-8818/2026.PJ31423

Recent Advances in the Relationship Between Hippocampus and Depression (2023-2025): Microscopic Mechanisms and Animal Models

Guanyu Chen

School of Science, Xi'an Jiaotong-Liverpool University, Suzhou, China
xjtlucgy21@163.com

Abstract. Major Depressive Disorder (MDD) is a pressing global psychiatric burden, with its pathophysiology closely linked to structural and functional abnormalities in the hippocampus. Recent scientific advances (2023-2025) have transcended macroscopic observations to delineate with precision the underlying molecular and cellular mechanisms. This overview summarizes the latest progress, focusing on two critical areas: neuroinflammation-mediated hippocampal damage and dysregulated neurogenesis and synaptic signaling pathways. The multifaceted roles of all glial subpopulations—microglia, astrocytes, and oligodendrocytes—in orchestrating neuroinflammation and myelinopathy are highlighted. Furthermore, we elaborate on the identification of novel pathways like the FGFR1–Notch–BDNF axis and the inhibitory protein Numb in regulating adult hippocampal neurogenesis (AHN), alongside the critical role of microglial-mediated synaptic pruning. The author reviews sophisticated animal models, including aged and genetically modified mice, used to validate these mechanisms and emerging therapeutic modalities, such as Numb inhibition and enhanced ERK signaling for long-lasting ketamine effects. These findings offer a refined understanding of the hippocampal neurobiology underlying MDD and identify promising therapeutic candidates for next-generation antidepressants, including Numb inhibition and ERK pathway modulation.

Keywords: Hippocampus, Major Depressive Disorder (MDD), Neuroinflammation, Adult Hippocampal Neurogenesis (AHN), Synaptic Plasticity, FGFR1–Notch–BDNF, Numb Protein

1. Introduction

Major Depressive Disorder (MDD) afflicts hundreds of millions of individuals worldwide, yet its complex etiology remains a significant challenge in psychiatric research and treatment [1]. Historically, the monoamine hypothesis dominated the field, but the suboptimal efficacy and delayed onset of monoaminergic agents, coupled with advancements in neuroimaging and molecular biology, have catalyzed a paradigm shift over the past decades toward neuroplasticity and structural cerebral alterations, particularly in the limbic system [2]. The hippocampus, a brain region critical for memory, emotion, and stress regulation, is consistently implicated in MDD pathophysiology,

DOI: 10.54254/2753-8818/2026.PJ31423

characterized by reduced volume and impaired neurogenesis [3]. This atrophy is not merely a structural anomaly but reflects profound molecular and cellular perturbations [4].

The current research landscape is undergoing rapid evolution, shifting from correlational observations toward the precise delineation of causal molecular and cellular events [5]. This is predominantly fueled by technological advancements in in vivo imaging, optogenetics, single-cell sequencing, and sophisticated genetic manipulation technologies. While the link between hippocampal dysfunction and MDD is robustly established, the exact molecular cascades and intercellular crosstalk that mediate this relationship remain incompletely elucidated. The focus has progressively shifted toward the non-neuronal components of the hippocampus, namely the glial cells (microglia, astrocytes, and oligodendrocytes), and the intricate intercellular signaling pathways that govern adult hippocampal neurogenesis (AHN) and synaptic plasticity [6].

This review seeks to offer a concise synthesis of the most impactful scientific advancements (2023-2025) pertaining to the hippocampus-MDD relationship. We center on two core domains: the precise microscopic mechanisms encompassing the multifaceted contributions of glial cells and key signaling pathways, and the validation of these findings via sophisticated animal models and cutting-edge techniques. By synthesizing this recent literature, this review seeks to pinpoint current research frontiers and highlight potential therapeutic targets, thereby contributing to the advancement of more effective and targeted interventions for MDD.

2. Microscopic mechanisms of hippocampal dysfunction in MDD

Recent studies have precisely pinpointed the molecular and cellular perturbations within the hippocampus that underlie the pathogenesis and progression of MDD. These mechanisms predominantly converge on chronic neuroinflammation, the failure of adult hippocampal neurogenesis (AHN), and compromised synaptic integrity.

2.1. Neuroinflammation and glial cell dysfunction

Neuroinflammation has emerged as a central pathological feature of MDD, exerting a profound impact on hippocampal function and plasticity. The latest research has detailed the specific and often interactive roles of all three major glial cell types and their associated inflammatory pathways.

2.1.1. Microglial polarization and inflammasome activation

Microglia, the resident immune cells of the central nervous system (CNS), play a dual role in maintaining brain homeostasis and mediating immune responses [7]. In MDD, there is a pronounced shift toward a pro-inflammatory (M1) phenotype [8]. This shift leads to the excessive secretion of pro-inflammatory cytokines, including Interleukin-1 beta (IL-1β), Tumor Necrosis Factor-alpha (TNF-α), and Interleukin-6 (IL-6), which are known to inhibit AHN and impair synaptic function. This microglial activation is substantiated by clinical evidence demonstrating elevated translocator protein (TSPO) binding, a marker of microglial activation, in the brains of MDD patients [9].

A key molecular mechanism orchestrating this neuroinflammatory response is the activation of the NLRP3 inflammasome [10]. This multi-protein complex, often triggered by damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), is activated in microglia and mediates the cleavage and secretion of potent inflammatory mediators including IL-1β. The activation of NLRP3, often mediated by the P2X7 receptor, is strongly correlated with depressive-like behaviors in animal models, suggesting that inhibiting this pathway could be a

DOI: 10.54254/2753-8818/2026.PJ31423

feasible antidepressant strategy [11]. Furthermore, microglial activation is increasingly linked to pathological synaptic pruning, where excessive pruning of dendritic spines in the hippocampus, particularly in the CA1 region, is promoted by chronic stress, leading to synaptic loss and behavioral deficits [12].

2.1.2. Astrocytic dysfunction and neurotransmitter homeostasis

Astrocytes are the most numerous glial cells and are essential for preserving blood-brain barrier (BBB) integrity, providing metabolic support to neurons, and regulating neurotransmitter homeostasis, particularly glutamate and GABA. Recent findings highlight that astrocytic dysfunction is a major contributor to MDD pathology [13]. Post-mortem analyses of MDD patients have consistently documented a decrease in the density and number of astrocytes, particularly in the hippocampus and prefrontal cortex, further supporting their critical role in the disorder's etiology.

In MDD, astrocytes exhibit reactive astrogliosis, which can encompass both neurotoxic (A1) and neuroprotective (A2) subtypes. Studies in 2023 and 2024 have focused on the role of astrocytic calcium signaling and its channel, Orai1, demonstrating that Orai1-mediated astrocyte reactivity is critical for inflammation-evoked depressive behaviors in mice [14]. Furthermore, defects in astrocytic ATP release have been shown to induce depressive-like behaviors [15]. The expression of Glucocorticoid Receptors (GR) is markedly enriched in astrocytes, and specific knockout of the GR gene in astrocytes can induce depressive-like phenotypes, underscoring their central role in mediating stress responses in the hippocampus [16]. The emerging concept of astrocyte-derived extracellular vesicles (EVs), which mediate intercellular communication by transferring protective factors to neurons, also represents a new frontier in understanding astrocyte-neuron communication in the context of MDD.

2.1.3. Oligodendrocyte pathology and myelination abnormalities

Oligodendrocytes (OLs) and their precursor cells (OPCs) are specialized in forming the myelin sheath, which is essential for rapid and efficient signal transmission. Recent research strongly implicates OL/myelin pathology in the hippocampus in MDD [17]. Clinical studies using diffusion tensor imaging (DTI) have demonstrated diminished white matter integrity and aberrant myelination patterns in MDD patients, suggesting that oligodendrocyte dysfunction is a significant pathological feature in the human brain.

Studies in 2024 and 2025 have shown that chronic stress, such as corticosterone exposure, can elicit myelin impairment and attenuate the proliferation and differentiation of OPCs in the hippocampus, leading to depressive-like behaviors [18]. This pathology is not limited to animal models; reduced intracortical myelin integrity has been observed in youths at risk for depression. The dysfunction of OL lineage cells is now considered an emerging player in the etiology of stress-related disorders. Importantly, the antidepressant paroxetine has been shown to mitigate corticosterone-induced myelin damage by promoting OPC proliferation and differentiation, suggesting that restoring myelin integrity is a key mechanism of action for certain antidepressant agents [19].

2.2. Dysregulated neurogenesis and synaptic signaling pathways

The failure of AHN and the disruption of synaptic integrity are inextricably intertwined in MDD pathogenesis. Recent breakthroughs have identified precise molecular axes that govern these

DOI: 10.54254/2753-8818/2026.PJ31423

processes, unveiling highly specific therapeutic candidates.

2.2.1. The FGFR1–Notch–BDNF axis and age-related depression

A significant study published in 2025 conducted a comprehensive dissection of a sequential signaling pathway critical for AHN [20]. The study demonstrated that Fibroblast Growth Factor Receptor 1 (FGFR1) is specifically overexpressed in the dentate gyrus (DG) of MDD patients. The research revealed a cascade: FGFR1–Notch–Brain-Derived Neurotrophic Factor (BDNF), which is essential for inducing AHN and mediating antidepressant effects. Crucially, this study unveiled a negative regulator of this axis: the protein Numb. Numb is known to suppress Notch signaling, and its expression was found to be markedly increased in the DG of elderly MDD patients, exhibiting a robust inverse correlation with hippocampal BDNF expression levels [20]. This discovery suggests that the age-related increase in Numb expression disrupts the protective FGFR1–Notch–BDNF pathway, establishing a direct molecular link between age-related Numb upregulation and the increased prevalence and severity of depression in the elderly. The precision of this finding allows for the development of highly targeted interventions aimed at restoring this specific neurogenic axis.

2.2.2. The FXR-CREB-BDNF axis and metabolic link

Another emerging area of focus is the role of the Farnesoid X Receptor (FXR), a nuclear receptor primarily known for regulating bile acid and lipid metabolism, which is also expressed in the hippocampus. Recent evidence indicates that FXR modulates the cAMP response element-binding protein (CREB)—BDNF signaling pathway [21]. CREB is a critical transcription factor that, when activated, promotes the expression of BDNF, thereby supporting neurogenesis and synaptic plasticity. The potential for FXR to influence this pathway establishes it as a novel, non-canonical therapeutic target for antidepressant drug development, possibly linking metabolic and neurological factors in MDD etiology [22]. Crucially, both the FGFR1–Notch–BDNF and FXR-CREB-BDNF axes converge on the regulation of BDNF, a master regulator of neurogenesis and synaptic plasticity, underscoring the central importance of BDNF signaling in MDD pathogenesis. This research direction underscores the increasing appreciation of the gut-brain axis and metabolic dysregulation in MDD.

2.2.3. Synaptic plasticity and microglial-mediated pruning

Synaptic plasticity, the ability of synapses to strengthen or weaken over time, is indispensable for learning, memory, and emotional homeostasis. MDD is characterized by a reduction in dendritic spine density and impaired long-term potentiation (LTP) in the hippocampus. These structural and functional abnormalities constitute the core pathological features of impaired synaptic plasticity, leading to impaired cognitive flexibility, emotional regulation, and memory function, which are hallmark symptoms of MDD.

Recent studies have unveiled a novel mechanism for this synaptic loss: pathological microglial-mediated synaptic pruning. Chronic stress can induce excessive pruning of excitatory synapses in the hippocampal CA1 region, culminating in anxiety- and depression-like behaviors. A 2025 study identified that chronic stress downregulates the expression of the protein DKK3 in CA1 neurons, which subsequently activates a Wnt-CX3CL1-CX3CR1 signaling pathway, leading to microglial over-activation and excessive synaptic elimination [23]. This finding represents a pivotal advance by establishing a precise molecular link between stress, microglial function, and synaptic loss in the

DOI: 10.54254/2753-8818/2026.PJ31423

hippocampus, advancing beyond the broad notion of "synaptic dysfunction" to a specific, targetable mechanism of "synaptic elimination".

3. Validation through sophisticated animal models and advanced techniques

Animal models are indispensable for establishing causality between microscopic mechanisms and behavioral phenotypes. The recent three years (2023–2025) have witnessed the refinement of established models and the development of more target-specific approaches, frequently integrating cutting-edge technologies.

3.1. Refinement of stress-induced models

Traditional stress models, such as Chronic Unpredictable Mild Stress (CUMS) and Repeated Social Defeat (RSD), remain pivotal to MDD preclinical research. These models are essential for establishing the causal link between chronic stress and core depressive behavioral phenotypes, such as anhedonia (loss of pleasure) and social avoidance—accompanied by impaired adult hippocampal neurogenesis (AHN) and enhanced hippocampal neuroinflammation.

A key recent development is the integration of genetic engineering with these stress models. For instance, utilization of CRISPR-Cas9 technology to generate Glucocorticoid Receptor (GR) gene knockout mice combined with chronic stress exposure enables the precise modeling of the HPA axis dysregulation and GR resistance observed in a subset of MDD patients. This combined approach affords a more stable and mechanistically relevant platform for investigating the crosstalk among stress hormones, hippocampal neurons, and depressive-like behaviors. Furthermore, application of single-cell sequencing on these models has enabled profiling of cell-type-specific gene expression in endothelial, microglial, and oligodendrocyte cells within the hippocampus, yielding an unprecedented level of granularity on the cellular response to stress.

3.2. Targeted models for specific mechanisms

The most notable progress in animal modeling involves the creation of models specifically designed to validate the newly discovered molecular pathways.

3.2.1. The aged depressive mouse model and numb inhibition

The discovery of Numb's role in age-related depression was directly corroborated in a corticosterone-induced aged depressive mouse model [20]. In these aged mice, Numb expression was elevated, mimicking the human post-mortem findings, and was accompanied by depressive-like behaviors. This model was then used to demonstrate that targeted intervention to restore the FGFR1–Notch–BDNF axis could effectively promote AHN and abrogate the depressive-like phenotype. This represents a significant step towards developing treatments tailored to age-specific MDD neuropathology, which is often refractory to standard antidepressants.

3.2.2. Optogenetics and in vivo pathway dissection

The 2025 study on the FGFR1–Notch–BDNF axis employed optogenetic approaches for the in vivo spatiotemporal delineation of this pathway. By selectively activating or inhibiting specific components of the cascade in discrete hippocampal subregions, the researchers were able to confirm the necessity and sufficiency of this signaling axis in mediating both the pathological and

DOI: 10.54254/2753-8818/2026.PJ31423

therapeutic outcomes. Similarly, the study on DKK3-mediated synaptic pruning utilized viral-mediated gene knockdown and overexpression in CA1 neurons to causally link DKK3 downregulation to microglial activation and subsequent behavioral deficits [10].

3.3. Advanced imaging and therapeutic validation

Advanced in vivo imaging techniques, such as two-photon microscopy, have been instrumental in visualizing dynamic cellular processes in real-time within the living brain. These methods have enabled the direct observation of stress-induced synaptic spine elimination and the restorative effects of novel therapeutic agents. For instance, the efficacy of ketamine, a rapid-acting antidepressant, has been linked to its ability to rapidly restore synaptic density. Recent research has shown that sustained ketamine effects are dependent on the activation of the ERK signaling pathway, which promotes synaptogenesis. This finding was validated using animal models where ERK signaling was pharmacologically manipulated, demonstrating a direct causal link between this pathway and the long-term antidepressant efficacy of ketamine.

4. Conclusion

The scientific landscape of MDD research has undergone a profound transformation, moving beyond macroscopic and correlational studies to the precise dissection of microscopic mechanisms within the hippocampus. The period between 2023 and 2025 has been particularly fruitful, yielding critical insights into the roles of neuroinflammation, glial cell dysfunction, and specific signaling pathways governing neurogenesis and synaptic plasticity. The identification of the FGFR1–Notch–BDNF axis and its age-dependent inhibitor Numb provides a novel framework for understanding and treating depression in the elderly. Concurrently, the elucidation of the DKK3-Wnt-CX3CL1-CX3CR1 pathway offers a specific molecular target for mitigating stress-induced synaptic loss. These discoveries, validated through sophisticated animal models and cutting-edge techniques, not only deepen our understanding of MDD's neurobiology but also pave the way for a new generation of targeted, mechanism-based antidepressants. The continued exploration of these pathways and the development of compounds that can modulate them hold immense promise for alleviating the global burden of this devastating disorder.

References

[1] GBD 2019 Diseases and Injuries Collaborators, 2020. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet, 396(10258), pp.1204-1222.

[2] Liu, B., Liu, J., Wang, M., Zhang, Y. and Li, L., 2017. From serotonin to neuroplasticity: evolvement of theories for major depressive disorder. Frontiers in cellular neuroscience, 11, p.305.

[3] Malykhin, N.V. and Coupland, N.J., 2015. Hippocampal neuroplasticity in major depressive disorder. Neuroscience, 309, pp.230-245.

[4] Tartt, A.N., Fulmore, C.A., Liu, Y., Furuya, K., Fessler, E.B., Hen, R., Sisti, J.A. and Drew, M.R., 2022. Dysregulation of adult hippocampal neuroplasticity in major depression: pathogenesis and therapeutic implications. Molecular psychiatry, 27(4), pp.1886-1896.

[5] Cui, L., Liu, Y., Li, C., Zhang, X., Li, Y., Zhang, J., Wang, Y., Wang, Z., Li, X., Zhang, Y. and Zhang, G., 2024. Major depressive disorder: hypothesis, mechanism, and treatment. Signal Transduction and Targeted Therapy, 9(1), p.100.

[6] Boku, S., Nakagawa, S., Toda, H. and Hishimoto, A., 2018. Neural basis of major depressive disorder: Beyond monoamine hypothesis. Psychiatry and clinical neurosciences, 72(1), pp.3-12.

DOI: 10.54254/2753-8818/2026.PJ31423

[7] Gao, C., Jiang, M., Lei, H., Liu, Y., Zhang, Y., Liu, S. and Li, B., 2023. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. Signal Transduction and Targeted Therapy, 8(1), p.359.
[8] Woźny-Rasała, I., Słotwiński, R., Słotwińska, S.M. and Słotwiński, J., 2025. NLRP3 Inflammasome in Stress-Related Neuropsychiatric Disorders: Mechanisms of Neuron–Microglia–Astrocyte Crosstalk, HPA Axis Dysregulation, and Potential Therapeutic Strategies. Biomolecules, 15(9), p.1344.
[9] Xia, X., Wang, R., Li, Y., Zhang, G. and Li, X., 2025. The central role of microglia in major depressive disorder and its potential as a therapeutic target. Frontiers in Behavioral Neuroscience, 19, p.1598178.
[10] Chen, C., Wang, Z., Zhang, J., He, W. and Chen, H., 2025. NLRP3 Inflammasome: A New Target for the Treatment of Depression. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders), 24(1), pp.1-1.
[11] Akcay, E., Tufan, A.E. and Unal, K., 2024. P2X7 receptors from the perspective of NLRP3 inflammasome pathway in depression: Potential role of cannabidiol. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 131, p.110949.
[12] Wang, J., Jin, Y., Wang, S., Zhang, M., Wang, X., Wang, Y., Wu, Y., Liu, J. and Song, C., 2023. Microglia-dependent excessive synaptic pruning leads to cognitive impairment in a mouse model of postoperative cognitive dysfunction. Journal of neuroinflammation, 20(1), p.1.
[13] González-Arias, C. and Perea, G., 2025. When the stars misfire: astrocytic dysfunctions in major depressive disorder. Neurochemical Research, pp.1-16.
[14] Novakovic, A., Singhal, G., Kumar, A., O'Buckley, S.C., O'Farrell, I., Singhal, S., Meyer, J.H. and Baune, B.T., 2023. Neuroinflammation and major depressive disorder. Frontiers in Cellular Neuroscience, 17, p.1504555.
[15] Cao, X., Li, L.P., Wang, Q., Wu, Q., Hu, H.H., Zhang, M., Fang, Y.Y., Zhang, J., Li, S.J., Xiong, W.C. and So, K.F., 2013. Astrocyte-derived ATP modulates depressive-like behaviors. Nature medicine, 19(6), pp.773-777.
[16] Lu, C.L., Wang, S.H., Chuang, J.Y., Chen, K.Y., Lin, Y.T., Hsu, C.Y., Chen, Y.H., Chen, Y.H., Huang, C.C., Hsu, K.S. and Wang, S.T., 2022. Glucocorticoid receptor–dependent astrocytes mediate stress vulnerability. Biological Psychiatry, 92(4), pp.294-305.
[17] Gao, C., Zu, S., Liu, Y., Wang, Z., Tian, S., Li, Y., Zhang, Y., Zhang, G. and Li, X., 2025. Oligodendrocyte lineage cells dysfunction in depression. Translational Psychiatry, 15(1), p.73.
[18] Kokkosis, A.G., Tsetsenis, T.N., Pan-Vazquez, A., Kretz, O., Hubrich, M., Feyerabend, T.B., Rister, B., Zhang, Z.J., Lie, D.C., Theis, F.J. and Nagappan, P.G., 2022. Chronic stress disrupts the homeostasis and progeny progression of oligodendroglial lineage cells, associating immune oligodendrocytes with prefrontal cortex hypomyelination. Molecular psychiatry, 27(7), pp.3047-3063.
[19] Bu, J., Wang, J., Liu, Y., Zhang, H., Wang, Z., Zhang, H. and Li, Q., 2025. Paroxetine ameliorates corticosterone-induced myelin damage by promoting the proliferation and differentiation of oligodendrocyte precursor cells. Neuroscience, 569, pp.46-57.
[20] Shin, J., Kim, D., Kim, H., Kim, K. and Lee, Y., 2025. Dysregulation of FGFR1 signaling in the hippocampus facilitates depressive disorder. Experimental & Molecular Medicine, pp.1-13.
[21] Hu, W., Wu, J., Ye, T., Chen, Z., Tao, J. and Tong, L., 2020. Farnesoid X receptor-mediated cytoplasmic translocation of CRTC2 disrupts CREB-BDNF signaling in hippocampal CA1 and leads to the development of depression-like behaviors in mice. International Journal of Neuropsychopharmacology, 23(10), pp.673-686.
[22] He, H., Guo, M., Ran, L. and Wang, Y., 2025. Research progress on the effect of hippocampal FXR regulation of CREB-BDNF signaling pathway on depression. Chinese Journal of Clinical Pharmacology and Therapeutics, 30(2), pp.220-225.
[23] Chen, X., Zhang, K., Li, Y., Wang, C., Lou, H. and Yu, S., 2025. Stress induces behavioral disorders by promoting microglial phagocytosis via decreasing neuronal Dkk3. Molecular Psychiatry, pp.1-14.