REVIEW

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Research progress on hippocampal neurogenesis in autism spectrum disorder

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ABSTRACT
Autism spectrum disorder (ASD) is a group of severe neurodevelopmental disorders with unclear etiology and significant heterogeneity that is emerging as a global public health concern. Increasing research suggests the involvement of hippocampal neurogenesis defects in the onset and development of ASD, drawing increasing amounts of attention to hippocampal neurogenesis issues in ASD. In this paper, we analyze relevant international studies on hippocampal neurogenesis in ASD, discuss the role of neurobiology in the pathogenesis of ASD, and explore the potential of improving hippocampal neurogenesis as a therapeutic approach for ASD. This review aims to provide new treatment perspectives and theoretical foundations for clinical practice.

KEYWORDS
Autism spectrum disorder, Hippocampal neurogenesis, Hippocampus, Neurological disorders

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by core symptoms such as social communication and interaction deficits, as well as restricted and repetitive behaviors, interests, and activities. In recent years, the prevalence of ASD has steadily increased, with the most recent report from the US Centers for Disease Control and Prevention (CDC) indicating that one in every 36 children aged 8 years has ASD.[1] ASD often appears during early childhood development and can persist throughout the lifespan, which places a heavy burden on families and society. However, due to the complexity of its etiology and the lack of clarity regarding its pathogenesis, there is currently no effective treatment specifically targeting the core symptoms of ASD.[2] Therefore, research into the mechanisms underlying ASD has become an urgent public health necessity. Despite the unclear and heterogeneous nature of the pathogenesis of ASD, common phenotypic features among different ASD patients suggest the existence of shared biological foundations, such as impaired neurogenesis in certain brain regions, disrupted functional connectivity, and excitatory/inhibitory imbalance.[3–5] The hippocampus, as an important region of the brain's limbic system, plays a crucial role in memory storage, learning, emotion, and spatial perception. Disruptions in hippocampal neurogenesis are closely associated with various psychiatric disorders, including depression, schizophrenia, and anxiety.[6,7] Additionally, the hippocampus is involved in social behavior, a core manifestation of ASD.[8] The initial symptoms of ASD often appear between 1 and 2 years of age, a critical period for hippocampal development.[9] Increasing evidence suggests that defects in hippocampal neurogenesis form the basis of behavioral phenotypes in individuals with ASD.[10] Relevant studies have shown that a reduction in hippocampal nerve cells can impair regional communication between the hippocampus and the prefrontal cortex (PFC) and that executive function deficits in ASD are related to low activity in the PFC. This suggests that communication interference between the hippocampus and the PFC may be a potential factor leading to abnormal neurophysiological activity and behavioral disorders.[11,12] Autistic patients show memory impairments across multiple domains, with episodic memory being particularly impaired, and functional magnetic resonance imaging (MRI) studies suggest that this may be due to reduced integrity of hippocampal connections.[11] In recent years, increased attention has been focused on hippocampal neurogenesis issues in ASD. This paper, through the analysis of research on hippocampal neurogenesis in ASD, discusses the role of neurobiology in the pathogenesis of ASD and explores the possibility of improving hippocampal neurogenesis as a therapeutic approach for ASD, aiming to provide new treatment perspectives and theoretical foundations for clinical practice.

NEUROGENESIS

Overview of neurogenesis

Neurogenesis, also referred to as neural regeneration, encompasses an intricate process involving the proliferation of neural stem cells (NSCs). These cells undergo both balanced and unbalanced division, ultimately giving rise to committed progenitor cells. Subsequently, these progenitor cells migrate to various regions, undergo continual plastic changes, establish synaptic connections with other neurons, and the whole process culminates in the generation of complete neural functionality. This intricate process also entails the continuous proliferation and differentiation of NSCs, resulting in the formation of new neurons, astrocytes, and oligodendrocytes. Adult neurogenesis pertains to the remarkable ability of specific brain regions in mammals, persisting from birth throughout the entire lifespan, to generate new endogenous NSCs. These NSCs undergo a transformative process, evolving into functional neurons that migrate to designated brain regions. Ultimately, these newly formed neurons integrate seamlessly into the structural and functional framework of the brain. Historically, the prevailing notion posited that neural cells within the adult mammalian brain lacked the capacity for renewal and were incapable of regeneration following damage or death. It was widely believed that neurogenesis primarily occurred during the embryonic period or in the early stages of postnatal development.[13] Currently, although the mechanisms governing neurogenesis remain largely elusive, the existence of adult neurogenesis has been substantiated. Neurogenesis is known to contribute, to some extent, to the plasticity observed in both the structure and function of the brain.[14]

Hippocampal neurogenesis

The hippocampus serves as an important region of the limbic system in the brain, and it participates in various physiological and pathological processes, including spatial learning, cognitive memory, anxiety, depression, fear memory, and episodic memory. Researchers have roughly divided the hippocampus into three parts based on the location of different genes: the dorsal hippocampus (anterior one third), intermediate hippocampus (middle one third), and ventral hippocampus (ventral one third).[15] The dorsal and ventral hippocampus play distinct roles.[16] The dorsal hippocampus contains place cells that encode spatial locations. It receives a large amount of visuospatial information projections, including from the dorsolateral entorhinal cortex and caudal entorhinal cortex, which in turn receive primary inputs from the perirhinal cortex and postrhinal cortex.[17] In brief, the dorsal hippocampus–hypothalamus complex, together with the retrosplenial cortex and anterior cingulate cortex, forms an important cortical network primarily responsible for cognitive processes such as spatial

learning, memory, navigation, and exploration. The ventral hippocampus has strong fiber connections with subcortical structures such as the rostral hypothalamus and amygdala, which are closely related to its functions.[18] The ventral hippocampus also receives inputs from the ventromedial entorhinal cortex, which in turn receives inputs primarily from the piriform cortex, subicular cortex, and periamygdaloid cortex. These connections suggest that the ventral hippocampus is associated with behaviors such as defense, social interaction, and emotions.[18]

Broadly speaking, the hippocampus includes the dentate gyrus (DG), the cornu ammonis (CA), the subiculum, and the hippocampal rudiment surrounding the corpus callosum. Based on cellular morphology, developmental differences between different cortical areas, and fiber arrangement, the CA can be further divided into CA1, CA2, CA3, and CA4 regions. The DG and CA are often collectively referred to as the hippocampus. The hippocampus belongs to the archipallium and is composed of three layers of cells. For example, the CA is composed of a molecular layer, pyramidal layer, and polymorphic layer, and the DG is composed of a molecular layer, granule cell layer, and polymorphic layer. The subgranular zone (SGZ) is considered a primary region for adult mammalian neurogenesis.[14,19,20] It contains three types of neural progenitor cells (NPCs). Type 1 cells, also known as radial glia-like NPCs, extend across the entire granule cell layer, with branches migrating into the inner molecular layer. These cells express biomarkers such as glial fibrillary acidic protein (GFAP), nestin, SRY-box transcription factor 2, and brain lipid-binding protein.[21] Although type 1 cells express GFAP, a molecular marker of astrocytes, their morphology and function differ significantly from those of mature astrocytes. Type 2 cells are intermediate progenitor cells derived from type 1 cells, including the 2a and 2b subtypes. Type 2 cells have short branches and do not express GFAP. Type 3 cells, differentiated from intermediate progenitor cells, are mature neurons expressing biomarkers such as doublecortin protein (DCX), neuronal differentiation factor, and polysialylated acid-neural cell adhesion molecule. Most type 3 cells survive and can differentiate into dentate granule neurons.[22] Dentate granule neurons express specific markers of mature neurons, including neuronal nuclear antigen, calbindin, and Prox1. These neurons extend their dendrites into the molecular layer, integrating into existing neuronal circuits.[23,24]

Regulation pathways of hippocampal neurogenesis

Neurogenesis in the DG region of the hippocampus extends throughout the entire lifespan of mammals. During each period, there is a varying degree of proliferation of NSCs, development of newborn neurons, and the generation of axons and dendrites, along with the enhancement of synaptic connections. This process is regulated by various factors.

In the brain, signals from the local stem cell niche and cell factors secreted by surrounding cells, such as neurotrophic factors, transcription factors, and neuropeptides, can influence the proliferation or differentiation of NSCs, thereby regulating neurogenesis. Neurotrophic factors are extracellular signaling proteins essential for determining the fate of neuronal cells, and they play critical roles in neurogenesis, synaptic formation, neural plasticity, and neuronal survival.[25,26] Currently, well-studied neurotrophic factors include nerve growth factor, brain-derived neurotrophic factor (BDNF), and neurotrophins 3 and 4/5 (Nt3, Nt4/5). BDNF mediates NSC proliferation and promotes the differentiation of NPCs into neurons and oligodendrocytes by activating the mitogen-activated protein kinase (MAPK) pathway.[27] BDNF also inhibits NSC apoptosis through the activation of the tyrosine protein kinase B receptor, activating both the MAPK and phosphatidylinositol 3-kinase (Pi3K) pathways.[28] Moreover, BDNF plays a crucial role in synaptic transmission and plasticity in the hippocampus, serving as a key regulatory factor for long-term potentiation, learning, and memory. Dysregulation of BDNF expression and abnormal signal transduction are hallmarks of various neurodevelopmental disorders, such as attention deficit hyperactivity disorder, Rett syndrome, and ASD.[29]

Some common signaling pathways, such as the Notch pathway, Wnt pathway, and Shh pathway, have been confirmed to play regulatory roles in different stages of adult hippocampal neurogenesis.[30–33] In the postnatal and adult brain, the Notch signaling pathway, as a fundamental signaling system, collaborates with the Wnt signaling protein, bone morphogenetic protein, and Shh signaling protein pathways to mediate the regulation of hippocampal neurogenesis and synaptic plasticity. These pathways play a crucial role in the formation and plasticity of hippocampal neuronal circuits.[31] Additionally, they are involved in determining neuronal cell fate, axon growth, dendrite pruning, and retraction, as well as the expression of neurotransmitters and ion channels, among other biological pathways.[34] In the mature nervous system, these proteins dynamically control synaptic function and plasticity while continuing to regulate the survival of neuronal cells.[31]

In addition, the expression of neuronal nuclear transcription factors, such as the cAMP-response element binding protein (CREB), has been implicated in the survival rate of immature neurons in the hippocampal region following ischemia.[35] Epigenetic modifications in the GABAergic system can also influence adult hippocampal neurogenesis in the offspring of prenatal chronically stressed rats.[36] All of these factors contribute to the regulation of hippocampal neurogenesis.

HIPPOCAMPAL NEUROGENESIS OF ASD

In addition to functions such as memory storage, learning, emotion, and spatial sense construction, the hippocampus also indirectly participates in social behavior.[8] When the connectivity integrity of the hippocampus decreases, the atrophy rate increases and neuronal function is impaired, resulting in memory defects. These memory defects can lead to abnormal social behavior and even social communication disorders, which are the core manifestations of ASD.[8] The initial symptoms of ASD in children usually appear at 1–2 years of age, which is also a critical period for the development of the hippocampus. During this stage, the newly generated neurons in the DG and CA3 regions fully mature, can connect with the cerebral cortex, and acquire typical adult morphology.[9] Furthermore, hippocampal neuron dysfunction is closely related to various mental illnesses such as depression, schizophrenia, and anxiety disorders, and ASD is often associated with these diseases.[6,7] Given the above phenomenon, it is suspected that alterations in the hippocampus may contribute to the development of ASD symptoms.

Hippocampal neurogenesis of ASD patients

The neuropathology of the hippocampus in ASD patients was first reported in a postmortem study conducted in 1980. Postmortem examinations were conducted on the brain tissue of four ASD subjects who died at the ages of 4, 14, 27, and 33 years, and they observed abnormally small and densely packed cells in the subiculum and CA1 region of the hippocampus.[37] Subsequent research on the hippocampus in ASD has confirmed the presence of neurodevelopmental defects in the hippocampus. Live MRI scans of individuals with ASD aged 2–46 years revealed significant anatomical abnormalities in the DG region of the hippocampus across different age groups.[38] The autopsy results of a study involving 13 autistic subjects (aged 4–60 years) revealed that four of the autistic subjects exhibited abnormal neuronal migration and abnormal neurogenesis in the DG region of the hippocampus. Additionally, four autistic subjects displayed local distortions in the cellular structure of the CA region, and two autistic subjects showed distortions in the DG.[39] Cellular experiments have shown that a novel miRNA-mediated pathway downstream of methyl-CpG binding protein 2 (MeCP2) that influences neurogenesis via interactions with central molecular hubs is linked to autism spectrum disorders caused by MeCP2 deficiency using both monolayer and three dimensional (cerebral organoid) patient-derived and MeCP2-deficient neuronal culture models.[40] The above studies all suggest a close relationship between hippocampal neurogenesis and ASD. These findings indicate that defects in hippocampal neurogenesis may underlie the abnormal behavioral phenotypes observed in patients with ASD.[10] Impairments in hippocampal neurogenesis in ASD patients primarily manifest as abnormal hippocampal volume and weakened functional connectivity within the hippocampus.

Children (aged 2–24 months) and adolescents (aged 4–18 years) with ASD may exhibit an increased hippocampal volume compared to that of age-matched normally developing healthy individuals, potentially due to pathological development or experience-dependent structural and functional plasticity.[41,42] Similar findings have also been observed in adults with ASD.[43] However, other research has reported that some ASD children (aged 8–14 years) may exhibit a reduced hippocampal volume or no significant differences compared to typically developing children.[44] In addition, some reports have documented asymmetry in the bilateral hippocampal volume development in some patients with ASD.[45,46] Some studies have found that the right hippocampal volume is larger in ASD subjects (aged 6.5–27 years) than in normal children.[45] On the other hand, other studies have found that the left hippocampal volume is larger in ASD subjects (aged 7–34 years) than in normal children.[46] The inconsistency in these findings may be attributed to characteristic differences in the samples, such as age, sex, race, and the presence of comorbidities such as developmental delays and cognitive impairments. Furthermore, similar to its phenotypic heterogeneity, the pathogenesis of ASD also exhibits heterogeneity, leading to variations in hippocampal volume development among different patients. Some studies have shown that compared to control individuals, children with ASD have reduced functional connectivity in the neural circuits of the parahippocampal gyrus on both sides, accelerated atrophy rates, and significantly impaired neuronal function, which can lead to social behavior issues and even social interaction difficulties.[47] Moreover, it has been confirmed that factors present in the blood of autistic patients markedly affect preprogrammed neurogenesis, neuronal proliferation, migration, differentiation, and circuit organization. A cell culture experiment revealed that serum from ASD children decreased the proliferation of NSCs in culture while promoting neuronal migration, the development of dendritic-bearing small neurons, and synaptic formation. Autoantibodies against NSCs, which may also influence neuronal maturation, were detected in the serum of ASD children.[48]

It is worth mentioning that although we observed differences in asymmetry among individuals with ASD and healthy controls, it is not clear which is the cause (asymmetry or ASD) and which is the effect. The critical period for the occurrence and development of ASD is 12–24 months of age, but little is known about hippocampal neurogenesis in ASD children in this age group. In the future, more clinical studies will be necessary to investigate hippocampal neurogenesis in ASD during this critical period.

Hippocampal neurogenesis of the ASD murine model

At present, research on the pathogenesis of ASD is still during the exploratory stage, and animal models provide preclinical tools for understanding the occurrence and development of ASD. There are various animals used for preclinical studies on ASD, including zebrafish, macaques, rats, and invertebrates such as drosophila melanogaster. Rodents are commonly used in various studies due to their advantages, such as low cost, short gestation period, and high litter size. There are various methods for constructing the ASD model. Currently, there are genetic ASD mice models, the idiopathic ASD model of BTBR mice, and biochemistry-induced ASD murine models (such as lipopolysaccharide, sodium valproate, nicotine, PM2.5, etc.).

Biochemistry-induced ASD murine model

The valproic acid (VPA) model accurately simulates the core symptoms of ASD and exhibits good reliability and validity in neurophysiology, which is comparable to postmortem reports from ASD patients.[49] A wealth of research suggests that ASD murine models induced by VPA may exhibit developmental abnormalities of the hippocampus. Luhach et al.[50] found that prenatal exposure to VPA in male Wistar rats led to a decrease in the expression levels of CREB, DCX, and BDNF in the hippocampus at postnatal day (PND) 48, indicating a reduction in hippocampal neurogenesis. A study which examined the ameliorating effect of alpha-glycosyl isoquercitrin on disrupted hippocampal neurogenesis in the DG in ASD rats induced by prenatal VPA exposure has shown that VPA-exposed offspring showed decreased numbers of type-2a and type-3 NPCs among granule cell lineage subpopulations at PND21, but there were no changes in the granule cell lineage subpopulations in response to VPA at PND63.[51] Watanabe et al.[52] have investigated the developmental exposure effect of VPA on postnatal hippocampal neurogenesis in accordance with the exposure scheme of OECD Test Guideline 426 adopted for developmental neurotoxicity in ASD rats induced by prenatal VPA exposure, which have found that developmental exposure to VPA mainly targets interneurons, followed by late (at PND77) influences on NPC proliferation in the SGZ and consequently increased granule cell layer neurons in rats hippocampus, but there is no difference at PND21. The inconsistency in research findings may be related to the exposure method of VPA. It is well known that the ventral hippocampus is closely associated with emotional/social behaviors through its connections with the amygdala, and these behaviors are significant clinical manifestations of ASD. Therefore, abnormal ventral hippocampal development may be more closely related to the development of ASD symptoms. In addition, hippocampal neurogenesis occurs throughout a person's lifetime but undergoes dynamic changes over time.[53] Therefore, the inconsistency in research results may also be explained by differences in the periods and subregions of the hippocampus examined by researchers. Investigating neuronal morphological rearrangement in the PFC, in the hippocampus, in the nucleus accumbens, and in the basolateral amygdala at three different ages: immediately after weaning (PND21), prepubertal (PND35) and postpubertal (PND70) ages, a reduced number of spines was observed in the pyramidal neurons of the dorsal hippocampus at PND70 and an increase in the dendritic spine density was observed in pyramidal neurons of the ventral hippocampus at all studied ages.[54] Additionally, nicotine is a nonselective agonist to nicotinic acetylcholine receptors, which are distributed in the entire brain. Prenatal nicotine exposure has been shown to cause behavioral changes in rodents, but the phenotypes are variable between reports. Zhou et al.[55] found a decrease in newborn neurons in the hippocampus at PND60, specifically in the ventral part by establishing prenatal nicotine exposure mice, which suggested that the specific down-regulation of BrdU-positive neurons in the ventral hippocampus may be involved in the neuronal mechanism underlying lowered social behaviors in ASD.

Furthermore, abnormal hippocampal neurogenesis has also been observed in mouse models of ASD during the early postnatal period. Yochum et al.[56] reported that at 12 and 24 hours after VPA exposure to PND14, the number of granule cells in the DG of the hippocampus of BALB/c mice was decreased due to VPA-induced apoptosis. Wang et al.[57] have investigated that the total number of EdU-positive cells in SGZ of ASD mice induced by prenatal PM2.5 exposure significantly decreased, and the proliferation of nerve cells decreased significantly due to PM2.5 exposure at PND14. VPA exposure during early postnatal development can model ASD. Cai et al.[58] have found that the early postnatal VPA-exposed mice exhibited impaired hippocampal neurogenesis, characterized by significantly decreased BrdU-labeled cells and DCX-positive immature cells in the SGZ at PND15, compared with the B6 mice.

Other ASD mouse models

Some inbred mouse strains, such as A/J, BALB/cByJ (BALB), BTBR T+Itpr3tf/J (BTBR), C58/J (C58), and 129S1/SvlmJ mice, can effectively replicate social deficits and repetitive behaviors, serving as spontaneous animal models for ASD.[59] Among them, BTBR mice exhibit high levels of social deficits and repetitive stereotyped behaviors, leaving fewer social scent marks during interactions, making them a more common and representative spontaneous ASD animal model. Studies have shown that BTBR mice exhibit defects in hippocampal neurogenesis during the early postnatal period.[58,60] Cai et al.[58] have found that there was a significant reduction of DCX-marked cells

in the SGZ of the BTBR mice compared with that of the B6 mice and the number of BrdU-labeled cells was significantly decreased in the SGZ of BTBR mice compared with that in B6 mice at PND15. Zhong et al.[60] observed a significant reduction in the number of neural NPCs in the DG of the hippocampus in BTBR mice using immunofluorescence, indicating a decrease in neurogenesis in the experimental group compared to the control group at PND6–8. Clinical trials have found that the critical period of human hippocampal development overlaps with the emergence of initial symptoms in patients with ASD.[9] Therefore, the significant finding of hippocampal neurogenesis defects in neonatal BTBR mice holds great significance in understanding the neuropathological mechanisms of ASD. Additionally, similar findings have also been observed in adolescent BTBR mice.[61,62]

In addition, some single-gene knockout models, such as Fragile X Mental Retardation 1 (*Fmr1*), *Shank3*, *Chd8*, *Neuroligin3*, Contactin Associated Protein–Like 2 (*Cntnap2*), and Cyclin–Dependent Kinase–Like 5 (*Cdkl5*), have been exhibited abnormalities in hippocampal neurogenesis.[63–66]

THE CURRENT RESEARCH STATUS OF TREATING ASD BASED ON THE HIPPOCAMPAL NEUROGENESIS THEORY

The pathological features of hippocampal neurogenesis defects in ASD continue to provide a theoretical basis for interventions aimed at regulating hippocampal neurogenesis to reconstruct hippocampal networks. The restoration of abnormal hippocampal neurogenesis holds promise as a potential therapeutic target for ASD, prompting an increasing number of studies exploring interventions that address these abnormalities. Recently, early postpartum drug treatments (such as curcumin and the liver X receptor agonist TO901317) were shown to promote the proliferation and differentiation of hippocampal NPCs in ASD mouse models, which may alleviate the inhibition of hippocampal neurogenesis, thereby partially alleviating the abnormal behavior and enhancing cognitive function.[58,60] Other drug treatments, including fluoxetine, and zinc water, can ameliorate social behavior in ASD mice by rescuing adult hippocampal neurogenesis.[62,66] Animal experiments and clinical studies have shown that the transplantation of mesenchymal stem cells or human amniotic epithelial cells has a positive effect on the treatment of ASD through the induction of neurotrophic factors and immunomodulation.[67,68]

However, regardless of the intervention method, it only partially improved rather than completely reversed the defects in hippocampal neurogenesis defects in ASD model mice. This suggests that the occurrence and development of ASD are the result of multifactorial interactions, with hippocampal neurogenesis defects being just one of many contributing factors. In addition, the clinical application of pro-neurogenic strategies in humans has yet to be demonstrated. In the future, additional large-scale preclinical and clinical studies are needed to determine the safety and efficacy of therapies targeting hippocampal neurogenesis for the treatment of ASD.

CONCLUSION

In summary, hippocampal neurogenesis defects have been confirmed in both ASD patients and ASD mouse models. However, the question arises as to whether these animal models, which mimic human ASD phenotypes, truly represent phenotypes identical to idiopathic conditions. Phenotypic studies suggest that while animal models can simulate ASD patient phenotypes to some extent, animal experiments cannot fully capture the complexity of human neural physiology. Undeniably, these animal models have demonstrated causal relationships between genetic variations, cellular biology, neural system heterogeneity, and phenotypic behavior, significantly advancing research into the pathogenic mechanisms of ASD and providing a theoretical basis for biological interventions to improve ASD-like behaviors. Notably, the function of the hippocampus overlaps with most of the clinical symptoms in patients with ASD, such as social interaction, memory, spatial reasoning, and emotions, but not all. There are few reports in the literature regarding the correlation between the hippocampus and restricted interests and repetitive behaviors, which are other core symptoms of autism. Some research suggests that repetitive behaviors are characterized by reduced cognitive flexibility.[69] In addition, some of the inflexible behaviors of patients with ASD may be linked to their atypical memory; therefore, it is possible that the hippocampus indirectly contributes to the repetitive behaviors of ASD patients through associative memory.[70] However, whether hippocampal neurogenesis defects are associated with repetitive behaviors requires further investigation. Therefore, the hippocampus may represent a critical component within a system of altered brain regions that work in tandem to contribute to the ASD phenotype, not the unique pathophysiology. Currently, most studies have been conducted on the entire hippocampus as a unit to measure the level of hippocampal neurogenesis in ASD patients or ASD animal models. However, to gain a more detailed understanding of the relationship between ASD and the hippocampus, as well as to scientifically recognize the neurophysiological mechanisms of ASD, future studies require exploration of the biological changes in different subregions of the hippocampus in ASD patients or ASD animal models. Furthermore, although a close correlation between hippocampal neurogenesis defects and the

occurrence and development of ASD has been confirmed, the specific molecular mechanisms and biological pathways associated with the regulation of neurogenic niches remain unclear. To comprehensively understand the changes in neurogenesis and neuronal differentiation associated with neurodevelopmental disorders, further detailed research is needed. Large-scale studies will continue to be necessary for a comprehensive exploration of these aspects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Maenner MJ, Warren Z, Williams AR, Amoakohene E, Bakian AV, Bilder DA, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2020. *MMWR Surveill Summ.* 2023;72:1-14. DOI:10.15585/mmwr.ss7202a1
2. McCracken JT, Anagnostou E, Arango C, Dawson G, Farchione T, Mantua V, et al. Drug development for autism spectrum disorder (ASD): progress, challenges, and future directions. *Eur Neuropsychopharmacol.* 2021;48:3-31. DOI:10.1016/j.euroneuro.2021.05.010
3. Angrand L, Masson JD, Rubio-Casillas A, Nosten-Bertrand M, Crépeaux G. Inflammation and autophagy: a convergent point between autism spectrum disorder (ASD)-related genetic and environmental factors: focus on aluminum adjuvants. *Toxics.* 2022;10:518. DOI:10.3390/toxics10090518
4. Lei J, Deng Y, Ma S. Downregulation of TGIF2 is possibly correlated with neuronal apoptosis and autism-like symptoms in mice. *Brain Behav.* 2022;12:e2610. DOI:10.1002/brb3.2610
5. Goel A, Portera-Cailliau C. Autism in the balance: elevated E-I ratio as a homeostatic stabilization of synaptic drive. *Neuron.* 2019;101:543-545. DOI:10.1016/j.neuron.2019.01.033
6. Guo L, Jiang ZM, Sun RX, Pang W, Zhou X, Du ML, et al. Repeated social defeat stress inhibits development of hippocampus neurons through mitophagy and autophagy. *Brain Res Bull.* 2022;182:111-117. DOI:10.1016/j.brainresbull.2022.01.009
7. Zuccoli GS, Reis-de-Oliveira G, Garbes B, Falkai P, Schmitt A, Nakaya HI, et al. Linking proteomic alterations in schizophrenia hippocampus to NMDAr hypofunction in human neurons and oligodendrocytes. *Eur Arch Psychiatry Clin Neurosci.* 2021;271:1579-1586. DOI:10.1007/s00406-021-01248-w
8. Meisner OC, Nair A, Chang SWC. Amygdala connectivity and implications for social cognition and disorders. *Handb Clin Neurol.* 2022;187:381-403. DOI:10.1016/B978-0-12-823493-8.00017-1
9. Gómez RL, Edgin JO. The extended trajectory of hippocampal development: implications for early memory development and disorder. *Dev Cogn Neurosci.* 2016;18:57-69. DOI:10.1016/j.dcn.2015.08.009
10. Liu C, Liu J, Gong H, Liu T, Li X, Fan X. Implication of hippocampal neurogenesis in autism spectrum disorder: pathogenesis and therapeutic implications. *Curr Neuropharmacol.* 2023;21:2266-2282. DOI:10.2174/1570159x21666221220155455
11. Banker SM, Gu X, Schiller D, Foss-Feig JH. Hippocampal contributions to social and cognitive deficits in autism spectrum disorder. *Trends Neurosci.* 2021;44:793-807. DOI:10.1016/j.tins.2021.08.005
12. Mateus-Pinheiro A, Patrício P, Alves ND, Martins-Macedo J, Caetano I, Silveira-Rosa T, et al. Hippocampal cytogenesis abrogation impairs inter-regional communication between the hippocampus and prefrontal cortex and promotes the time-dependent manifestation of emotional and cognitive deficits. *Mol Psychiatry.* 2021;26:7154-7166. DOI:10.1038/s41380-021-01287-8
13. Fares J, Bou Diab Z, Nabha S, Fares Y. Neurogenesis in the adult hippocampus: history, regulation, and prospective roles. *Int J Neurosci.* 2019;129:598-611. DOI:10.1080/00207454.2018.1545771
14. Abbott LC, Nigussie F. Adult neurogenesis in the mammalian dentate gyrus. *Anat Histol Embryol.* 2020;49:3-16. DOI:10.1111/ahe.12496
15. Lee AR, Kim JH, Cho E, Kim M, Park M. Dorsal and ventral hippocampus differentiate in functional pathways and differentially associate with neurological disease-related genes during postnatal development. *Front Mol Neurosci.* 2017;10:331. DOI:10.3389/fnmol.2017.00331
16. Strange BA, Witter MP, Lein ES, Moser EI. Functional organization of the hippocampal longitudinal axis. *Nat Rev Neurosci.* 2014;15:655-669. DOI:10.1038/nrn3785
17. Bradfield LA, Leung BK, Boldt S, Liang S, Balleine BW. Goal-directed actions transiently depend on dorsal hippocampus. *Nat Neurosci.* 2020;23:1194-1197. DOI:10.1038/s41593-020-0693-8
18. Kim J, Castro L, Wasserman EA, Freeman JH. Dorsal hippocampus is necessary for visual categorization in rats. *Hippocampus.* 2018;28:392-405. DOI:10.1002/hipo.22839
19. Kumari E, Velloso FJ, Nasuhidehnavi A, Somasundaram A, Savanur VH, Buono KD, et al. Developmental IL-6 exposure favors production of PDGF-responsive multipotential progenitors at the expense of neural stem cells and other progenitors. *Stem Cell Reports.* 2020;14:861-875. DOI:10.1016/j.stemcr.2020.03.019
20. Storer MA, Gallagher D, Fatt MP, Simonetta JV, Kaplan DR, Miller FD. Interleukin-6 regulates adult neural stem cell numbers during normal and abnormal post-natal development. *Stem Cell Reports.* 2018;10:1464-1480. DOI:10.1016/j.stemcr.2018.03.008
21. Bonaguidi MA, Wheeler MA, Shapiro JS, Stadel RP, Sun GJ, Ming GL, et al. In vivo clonal analysis reveals self-renewing and multipotent adult neural stem cell characteristics. *Cell.* 2011;145:1142-1155. DOI:10.1016/j.cell.2011.05.024
22. Gao Z, Ure K, Ables JL, Lagace DC, Nave KA, Goebbels S, et al. Neurod1 is essential for the survival and maturation of adult-born neurons. *Nat Neurosci.* 2009;12:1090-1092. DOI:10.1038/nn.2385

23. Lavado A, Lagutin OV, Chow LM, Baker SJ, Oliver G. Prox1 is required for granule cell maturation and intermediate progenitor maintenance during brain neurogenesis. *PLoS Biol.* 2010;8:e1000460. DOI:10.1371/journal.pbio.1000460
24. Zhao C, Teng EM, Summers RG, Jr MingGL, Gage FH. Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. *J Neurosci.* 2006;26:3-11. DOI:10.1523/JNEUROSCI.3648-05.2006
25. Hazari MS, Pan JH, Myers AC. Nerve growth factor acutely potentiates synaptic transmission in vitro and induces dendritic growth in vivo on adult neurons in airway parasympathetic ganglia. *Am J Physiol Lung Cell Mol Physiol.* 2007;292:L992-1001. DOI:10.1152/ajplung.00216.2006
26. Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron.* 2010;66:198-204. DOI:10.1016/j.neuron.2010.03.035
27. Chen BY, Wang X, Wang ZY, Wang YZ, Chen LW, Luo ZJ. Brain-derived neurotrophic factor stimulates proliferation and differentiation of neural stem cells, possibly by triggering the Wnt/β-catenin signaling pathway. *J Neurosci Res.* 2013;91:30-41. DOI:10.1002/jnr.23138
28. Numakawa T, Suzuki S, Kumamaru E, Adachi N, Richards M, Kunugi H. BDNF function and intracellular signaling in neurons. *Histol Histopathol.* 2010;25:237-258. DOI:10.14670/HH-25.237
29. Camuso S, La Rosa P, Fiorenza MT, Canterini S. Pleiotropic effects of BDNF on the cerebellum and hippocampus: implications for neurodevelopmental disorders. *Neurobiol Dis.* 2022;163:105606. DOI:10.1016/j.nbd.2021.105606
30. Bagheri-Mohammadi S. Adult neurogenesis and the molecular signalling pathways in brain: the role of stem cells in adult hippocampal neurogenesis. *Int J Neurosci.* 2022;132:1165-1177. DOI:10.1080/00207454.2020.1865953
31. Luan Y, Zhang H, Ma K, Liu Y, Lu H, Chen X, et al. CCN3/NOV regulates proliferation and neuronal differentiation in mouse hippocampal neural stem cells via the activation of the notch/PTEN/AKT pathway. *Int J Mol Sci.* 2023;24:10324. DOI:10.3390/ijms241210324
32. Zhao Y, Wang G, Wei Z, Li D, Wnt MorshediM. Wnt, notch signaling and exercise: what are their functions. *Hum Cell.* Published online: Feb 22, 2024. DOI:10.1007/s13577-024-01036-3
33. Arredondo SB, Guerrero FG, Herrera-Soto A, Jensen-Flores J, Bustamante DB, Oñate-Ponce A, et al. Wnt5a promotes differentiation and development of adult-born neurons in the hippocampus by noncanonical Wnt signaling. *Stem Cells.* 2020;38:422-436. DOI:10.1002/stem.3121
34. Qiao J, Zhao J, Chang S, Sun Q, Liu N, Dong J, et al. MicroRNA-153 improves the neurogenesis of neural stem cells and enhances the cognitive ability of aged mice through the notch signaling pathway. *Cell Death Differ.* 2020;27:808-825. DOI:10.1038/s41418-019-0388-4
35. Yoo DY, Jung HY, Kim W, Hahn KR, Kwon HJ, Nam SM, et al. Entacapone promotes hippocampal neurogenesis in mice. *Neural Regen Res.* 2021;16:1005-1110. DOI:10.4103/1673-5374.300447
36. Zhong H, Rong J, Zhu C, Liang M, Li Y, Zhou R. Epigenetic modifications of GABAergic interneurons contribute to deficits in adult hippocampus neurogenesis and depression-like behavior in prenatally stressed mice. *Int J Neuropsychopharmacol.* 2020;23:274-285. DOI:10.1093/ijnp/pyaa020
37. Williams RS, Hauser SL, Purpura DP, DeLong GR, Swisher CN. Autism and mental retardation: neuropathologic studies performed in four retarded persons with autistic behavior. *Arch Neurol.* 1980;37:749-753. DOI:10.1001/archneur.1980.00500610029003
38. Saitoh O, Karns CM, Courchesne E. Development of the hippocampal formation from 2 to 42 years: mRI evidence of smaller area dentata in autism. *Brain.* 2001;124:1317-1324. DOI:10.1093/brain/124.7.1317
39. Wegiel J, Kuchna I, Nowicki K, Imaki H, Wegiel J, Marchi E, et al. The neuropathology of autism: defects of neurogenesis and neuronal migration, and dysplastic changes. *Acta Neuropathol.* 2010;119:755-770. DOI:10.1007/s00401-010-0655-4
40. Mellios N, Feldman DA, Sheridan SD, Ip J, Kwok S, Amoah SK, et al. MeCP2-regulated miRNAs control early human neurogenesis through differential effects on ERK and AKT signaling. *Mol Psychiatry.* 2018;23:1051-1065. DOI:10.1038/mp.2017.86
41. Sussman D, Leung RC, Vogan VM, Lee W, Trelle S, Lin S, et al. The autism puzzle: diffuse but not pervasive neuroanatomical abnormalities in children with ASD. *Neuroimage Clin.* 2015;8:170-179. DOI:10.1016/j.nicl.2015.04.008
42. Li G, Chen MH, Li G, Wu D, Lian C, Sun Q, et al. Volumetric analysis of amygdala and hippocampal subfields for infants with autism. *J Autism Dev Disord.* 2023;53:2475-2489. DOI:10.1007/s10803-022-05535-w
43. Maier S, Tebartz van Elst L, Beier D, Ebert D, Fangmeier T, Radtke M, et al. Increased hippocampal volumes in adults with high functioning autism spectrum disorder and an IQ>100: a manual morphometric study. *Psychiatry Res.* 2015;234:152-155. DOI:10.1016/j.pscychresns.2015.08.002
44. Arutiunian V, Davydova E, Pereverzeva D, Sorokin A, Tyushkevich S, Mamokhina U, et al. Reduced grey matter volume of amygdala and hippocampus is associated with the severity of autistic symptoms and language abilities in school-aged children with Autism Spectrum Disorder: an exploratory study. *Brain Struct Funct.* 2023;228:1573-1579. DOI:10.1007/s00429-023-02660-9
45. Xu Q, Zuo C, Liao S, Long Y, Wang Y. Abnormal development pattern of the amygdala and hippocampus from childhood to adulthood with autism. *J Clin Neurosci.* 2020;78:327-332. DOI:10.1016/j.jocn.2020.03.049
46. Richards R, Greimel E, Kliemann D, Koerte IK, Schulte-Körne G, Reuter M, et al. Increased hippocampal shape asymmetry and volumetric ventricular asymmetry in autism spectrum disorder. *Neuroimage Clin.* 2020;26:102207. DOI:10.1016/j.nicl.2020.102207
47. Pagni BA, Walsh M, Ofori E, Chen K, Sullivan G, Alvar J, et al. Effects of age on the hippocampus and verbal memory in adults with autism spectrum disorder: longitudinal versus

cross-sectional findings. *Autism Res.* 2022;15:1810-1823. DOI:10.1002/aur.2797
48. Mazur-Kolecka B, Cohen IL, Jenkins EC, Kaczmarski W, Flory M, Frackowiak J. Altered development of neuronal progenitor cells after stimulation with autistic blood sera. *Brain Res.* 2007;1168:11-20. DOI:10.1016/j.brainres.2007.06.084
49. Sawada K, Kamiya S, Aoki I. The proliferation of dentate gyrus progenitors in the ferret hippocampus by neonatal exposure to valproic acid. *Front Neurosci.* 2021;15:736313. DOI:10.3389/fnins.2021.736313
50. Luhach K, Kulkarni GT, Singh VP, Sharma B. Attenuation of neurobehavioural abnormalities by papaverine in prenatal valproic acid rat model of ASD. *Eur J Pharmacol.* 2021;890:173663. DOI:10.1016/j.ejphar.2020.173663
51. Takashima K, Okano H, Ojiro R, Tang Q, Takahashi Y, Ozawa S, et al. Continuous exposure to alpha-glycosyl isoquercitrin from gestation ameliorates disrupted hippocampal neurogenesis in rats induced by gestational injection of valproic acid. *Neurotox Res.* 2022;40:2278-2296. DOI:10.1007/s12640-022-00574-8
52. Watanabe Y, Murakami T, Kawashima M, Hasegawa-Baba Y, Mizukami S, Imatanaka N, et al. Maternal exposure to valproic acid primarily targets interneurons followed by late effects on neurogenesis in the hippocampal dentate gyrus in rat offspring. *Neurotox Res.* 2017;31:46-62. DOI:10.1007/s12640-016-9660-2
53. Sorrells SF, Paredes MF, Cebrian-Silla A, Sandoval K, Qi D, Kelley KW, et al. Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. *Nature.* 2018;555:377-381. DOI:10.1038/nature25975
54. Bringas ME, Carvajal-Flores FN, López-Ramírez TA, Atzori M, Flores G. Rearrangement of the dendritic morphology in limbic regions and altered exploratory behavior in a rat model of autism spectrum disorder. *Neuroscience.* 2013;241:170-187. DOI:10.1016/j.neuroscience.2013.03.030
55. Zhou M, Qiu W, Ohashi N, Sun L, Wronski ML, Kouyama-Suzuki E, et al. Deep-learning-based analysis reveals a social behavior deficit in mice exposed prenatally to nicotine. *Cells.* 2024;13:275. DOI:10.3390/cells13030275
56. Yochum CL, Dowling P, Reuhl KR, Wagner GC, Ming X. VPA-induced apoptosis and behavioral deficits in neonatal mice. *Brain Res.* 2008;1203:126-132. DOI:10.1016/j.brainres.2008.01.055
57. Wang T, Zhang T, Sun L, Li W, Zhang C, Yu L, et al. Gestational B-vitamin supplementation alleviates PM(2.5)-induced autism-like behavior and hippocampal neurodevelopmental impairment in mice offspring. *Ecotoxicol Environ Saf.* 2019;185:109686. DOI:10.1016/j.ecoenv.2019.109686
58. Cai Y, Zhong H, Li X, Xiao R, Wang L, Fan X. The liver X receptor agonist TO901317 ameliorates behavioral deficits in two mouse models of autism. *Front Cell Neurosci.* 2019;13:213. DOI:10.3389/fncel.2019.00213
59. Moy SS, Nadler JJ, Young NB, Perez A, Holloway LP, Barbaro RP, et al. Mouse behavioral tasks relevant to autism: phenotypes of 10 inbred strains. *Behav Brain Res.* 2007;176:4-20. DOI:10.1016/j.bbr.2006.07.030
60. Zhong H, Xiao R, Ruan R, Liu H, Li X, Cai Y, et al. Neonatal curcumin treatment restores hippocampal neurogenesis and improves autism-related behaviors in a mouse model of autism. *Psychopharmacology (Berl).* 2020;237:3539-3552. DOI:10.1007/s00213-020-05634-5
61. Stephenson DT, O'Neill SM, Narayan S, Tiwari A, Arnold E, Samaroo HD, et al. Histopathologic characterization of the BTBR mouse model of autistic-like behavior reveals selective changes in neurodevelopmental proteins and adult hippocampal neurogenesis. *Mol Autism.* 2011;2:7. DOI:10.1186/2040-2392-2-7
62. Zhang L, Xu X, Ma L, Wang X, Jin M, Li L, et al. Zinc water prevents autism-like behaviors in the BTBR mice. *Biol Trace Elem Res.* 2023;201:4779-4792. DOI:10.1007/s12011-022-03548-1
63. Cope EC, Briones BA, Brockett AT, Martinez S, Vigneron PA, Opendak M, et al. Immature neurons and radial glia, but not astrocytes or microglia, are altered in adult Cntnap2 and Shank3 mice, models of autism. *eNeuro.* 2016;3:ENEURO.0919-16.2016. DOI:10.1523/ENEURO.0196-16.2016
64. Pinar C, Yau SY, Sharp Z, Shamei A, Fontaine CJ, Meconi AL, et al. Effects of voluntary exercise on cell proliferation and neurogenesis in the dentate gyrus of adult Fmr1 knockout mice. *Brain Plast.* 2018;4:185-195. DOI:10.3233/BPL-170052
65. Dong C, Zhao C, Chen X, Berry K, Wang J, Zhang F, et al. Conserved and distinct functions of the autism-related chromatin remodeler Chd8 in embryonic and adult forebrain neurogenesis. *J Neurosci.* 2022;42:8373-8392. DOI:10.1523/JNEUROSCI.2400-21.2022
66. Gioia R, Seri T, Diamanti T, Fimmanò S, Vitale M, Ahlenius H, et al. Adult hippocampal neurogenesis and social behavioural deficits in the R451C Neuroligin3 mouse model of autism are reverted by the antidepressant fluoxetine. *J Neurochem.* 2023;165:318-333. DOI:10.1111/jnc.15753
67. Liang Y, Duan L, Xu X, Li X, Liu M, Chen H, et al. Mesenchymal stem cell-derived exosomes for treatment of autism spectrum disorder. *ACS Appl Bio Mater.* 2020;3:6384-6393. DOI:10.1021/acsabm.0c00831
68. Zhang R, Cai Y, Xiao R, Zhong H, Li X, Guo L, et al. Human amniotic epithelial cell transplantation promotes neurogenesis and ameliorates social deficits in BTBR mice. *Stem Cell Res Ther.* 2019;10:153. DOI:10.1186/s13287-019-1267-0
69. Lopez BR, Lincoln AJ, Ozonoff S, Lai Z. Examining the relationship between executive functions and restricted, repetitive symptoms of Autistic Disorder. *J Autism Dev Disord.* 2005;35:445-460. DOI:10.1007/s10803-005-5035-x
70. Hashimoto T, Yokota S, Matsuzaki Y, Kawashima R. Intrinsic hippocampal functional connectivity underlying rigid memory in children and adolescents with autism spectrum disorder: a case-control study. *Autism.* 2021;25:1901-1912. DOI:10.1177/13623613211004058

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