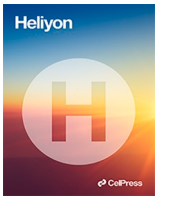
Heliyon 11 (2025) e42668

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Multimodal insights into adult neurogenesis: An integrative review of multi-omics approaches

Jin Li [a,b,1], Leyi Huang [a,1], Wenjie Xiao [a], Jingyi Kong [a], Minghua Hu [c], Aihua Pan [a], Xiaoxin Yan [a], Fulian Huang [b,*], Lily Wan [a,**]

[a] Department of Anatomy and Neurobiology, Xiangya School of Basic Medicine, Central South University, Changsha, Hunan Province, China
[b] Yiyang Medical College, Yiyang, Hunan Province, China
[c] Hunan Key Laboratory of the Research and Development of Novel Pharmaceutical Preparations, Changsha Medical University, Changsha, Hunan Province, China

ARTICLE INFO

Keywords:
Adult neurogenesis
Genomics
Metabolomics
Proteomics
Transcriptomics
Microbiomics
Epigenomics

ABSTRACT

Adult neural stem cells divide to produce neurons that migrate to preexisting neuronal circuits in a process named adult neurogenesis. Adult neurogenesis is one of the most exciting areas of current neuroscience, and it may be involved in a range of brain functions, including cognition, learning, memory, and social and behavior changes. While there is a growing number of multi-omics studies on adult neurogenesis, generalized analyses from a multi-omics perspective are lacking. In this review, we summarize studies related to genomics, metabolomics, proteomics, epigenomics, transcriptomics, and microbiomics of adult neurogenesis, and then discuss their future research priorities and potential neighborhoods. This will provide theoretical guidance and new directions for future research on adult neurogenesis.

1. Introduction

The overwhelming majority of mammalian species are capable of adult hippocampal neurogenesis, as demonstrated by numerous studies conducted over the past 20 years [1]. Adult neurogenesis is the process by which neural stem cells (NSCs) or neuronal precursor cells (NPCs) proliferate, migrate, and differentiate into new neurons under certain conditions in the adult brain, maturing and eventually integrating into functional neural circuits [2] (Fig. 1). In rats, adult neurogenesis was thought to occur predominantly in the subventricular zone (SVZ) of the lateral ventricle wall and the subgranular zone (SGZ) of the dentate gyrus forming the hippocampus [3], which is involved in olfactory and spatial learning and memory. Similar neurogenesis has been found in humans and appears to occur in other regions, such as the striatum [4]. Adult hippocampal neurogenesis (AHN) is also important for cognitive function, emotion regulation, and behavioral processes. The impairment of AHN has been implicated in the pathogenesis of many psychiatric and neurological disorders affecting different age groups. An understanding of the mechanism of adult neurogenesis will create the basis for finding relevant biomarkers and help provide new ideas for drug development.

The existence of adult neurogenesis and its associated mechanisms took a long time to prove. Prior to the 20th century, it was generally believed that nerve cells were terminal cells without the ability to regenerate and that the adult brain could not produce new

* Corresponding author.
** Corresponding author.
E-mail addresses: hflscience@126.com (F. Huang), wanll1203@csu.edu.cn (L. Wan).
[1] Authors contribute equally to this work.

https://doi.org/10.1016/j.heliyon.2025.e42668
Received 5 September 2024; Received in revised form 23 December 2024; Accepted 11 February 2025
Available online 13 February 2025

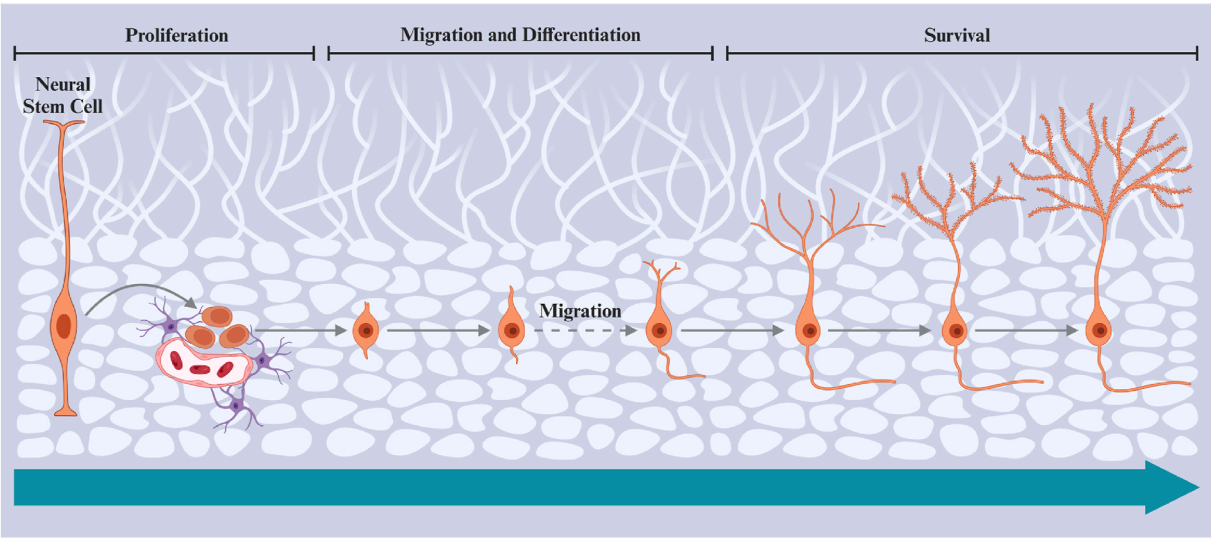


Fig. 1. Adult neurogenesis process pattern in hippocampus.

neurons. In 1912, Allen et al. discovered mitotic cell division in the lateral ventricles of 120-day-old rats, suggesting for the first time that neuronal neogenesis could occur in the adult mammalian brain. Altman et al. identified new neurons in the hippocampal dentate gyrus of the adult rat brain using thymidine nucleoside-H3 labeling, providing radiological and histological evidence for the generation of new neurons in the hippocampus [5,6]. Immunofluorescence confocal microscopy in the late 1980s and early 1990s revealed that 5-bromodeoxyuridine nucleoside (BrdU), used to label mitotically active cells, can be combined with neuronal and/or glial markers to determine cell phenotypes [7,8]. With the development of technology, adult neurogenesis has been confirmed to exist in the central nervous system of mammals, especially in the SVZ and hippocampus [9]. Related historical developments are summarized in Fig. 2.

Over the past few decades, multi-omics techniques have revolutionized biomedical research [10]. It includes genomics, transcriptomics, epigenomics, proteomics, metabolomics, microbiomics, and other fields. These data are known as "multi-omics" data [11]. The integration of multi-omics data can promote the systematic and thorough understanding of complex biological processes [12], which has the potential to provide new biological insights into disease mechanisms [13]. Integrated multi-omics analysis helps to assess the flow of information from one omics level to another, bridging the gap from genotype to phenotype, while its ability to study biological phenomena as a whole allows for a deeper study of the mechanisms of and therefore can contribute to better treatment and prevention [14,15]. In this paper, we analyze a multi-omics study of adult neurogenesis, reviewing the results and developments from six omics aspects (Fig. 3) and providing a reference for future studies.

2. Search strategy and selection criteria

We searched PubMed and Medline for papers published before July 2024, using the following terms: "Adult Neurogenesis", "Genomics", "Transcriptomics", "Proteomics", "Metabolomics", "Microbiomics" and "Epigenomics" in different combinations (Table 1). Additional articles were identified by reviewing the reference lists of key papers in the field. There were no language restrictions. Final references were selected based on originality, currency, impact, and relevance to the broad scope of this review.

2.1. Genomics

This section delves into the genomic landscape of adult neurogenesis, focusing on critical processes such as neural stem cell proliferation, neuronal differentiation, synaptic plasticity, and neurodevelopment. Selection of genes for this study is based on their significance to neurodevelopment and their potential impact on adult neurogenesis. Additionally, some genes are linked to diseases or conditions that may affect neurogenesis, making them focal points of research that illuminate the mechanisms (as detailed in Table 2).

In the context of neural stem cell proliferation, *Sox11* and *Sox4* are co-expressed in adult hippocampal neural stem cells, as well as in IIb and III intermediate progenitor cells and immature neurons [16]. The knockdown of *Sox11* and *Sox4* significantly inhibits adult hippocampal neurogenesis [17–19]. Similarly, *SRRM4* knockout in embryonic ventricular zones results in a reduced number of Pax6+ cells and post-mitotic NeuN + neurons [20]. *Tdrd3* knockout mice demonstrate enhanced neuronal complexity but reduced myelination, highlighting its role in neurodevelopment [21]. Regarding neuronal differentiation, *SRD5A3* is involved in lipid-linked oligosaccharide synthesis, and mutations in this gene lead to defects that inhibit neurogenesis [22,23]. *PMM2* mutations are associated with glycosylation diseases, and mouse models with these mutations exhibit neurodevelopmental defects [24]. The deletion of *PTBP1* results in the premature differentiation of radial glial cells into neurons, thereby depleting the radial glial cell pool [25].

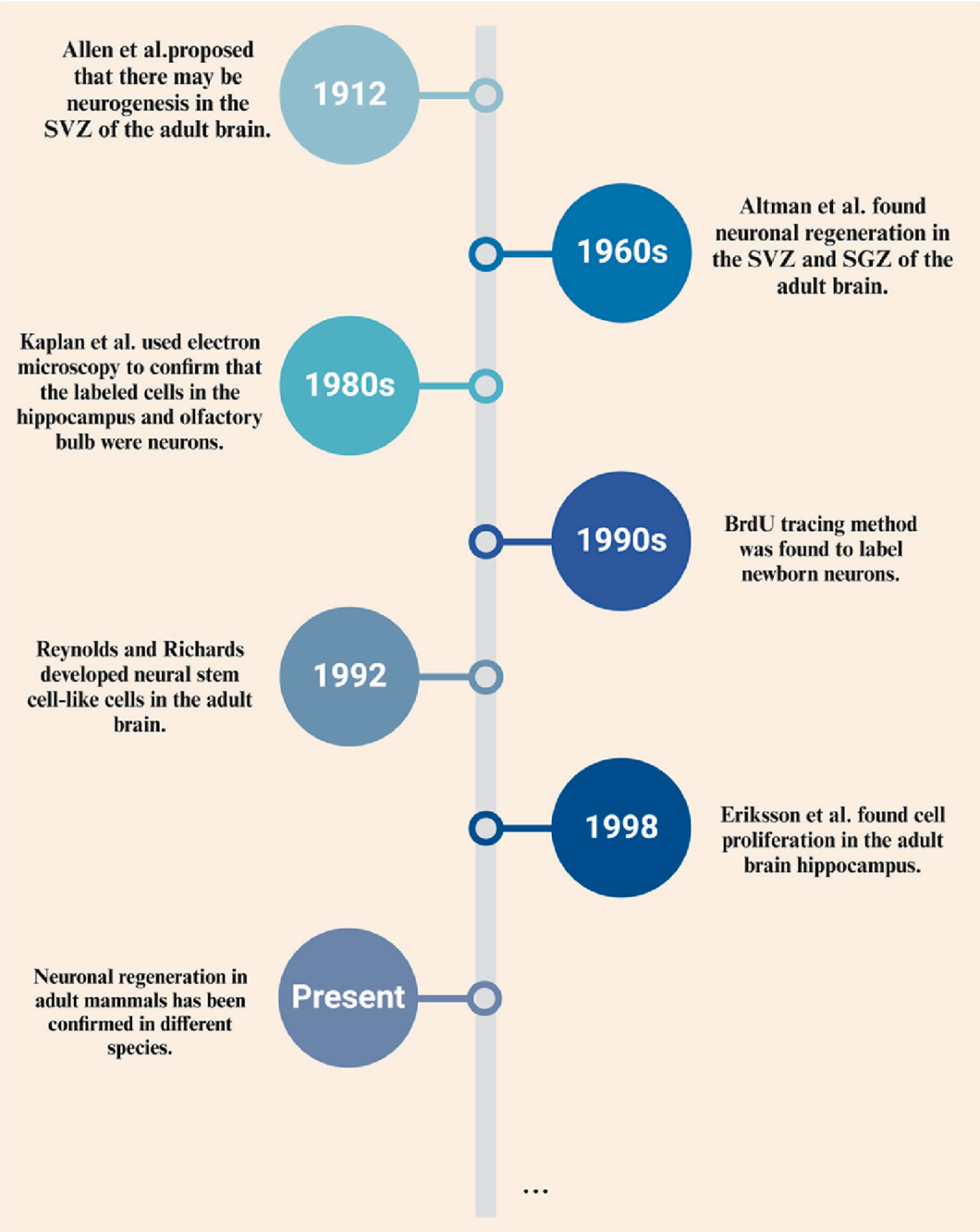


Fig. 2. Major discoveries in the study of adult neurogenesis.

In terms of synaptic plasticity, *Gas1* is co-localized with NeuroD1 in the neocortex, hippocampal dentate gyrus, and cerebellar external granular layer, and is a direct target of NeuroD1 [26]. *Gas1* plays a role in neurodevelopment, with its expression regulated by NeuroD1 [27]. Additionally, BPA, an endocrine disruptor found in human urine samples, affects fetal brain development [28]. BPA exposure leads to the upregulation of *Sxt1a* in mice, suggesting a long-term impact on synaptic plasticity [29].

Other related genes also play significant roles in adult neurogenesis. *CSTB* mutations cause progressive myoclonic epilepsy (PME) and result in hippocampal neurogenesis defects in mouse models [30]. *DIAPH3* mutations affect filopodia formation, essential for neocortical neuropil development and neurogenesis [31]. *Snhg11* knockout mice exhibit deficits in dentate gyrus synaptic plasticity and neurogenesis [32]. *Derlin-1* deficiency impairs neural stem cell proliferation and differentiation, thereby affecting neurogenesis [33]. Similarly, *Hdac8* knockout impairs the proliferation and differentiation of neural progenitor cells (NPCs), impacting neurogenesis [34]. In conclusion, genomic studies reveal that numerous genes are involved in adult neurogenesis, encompassing neural stem cell

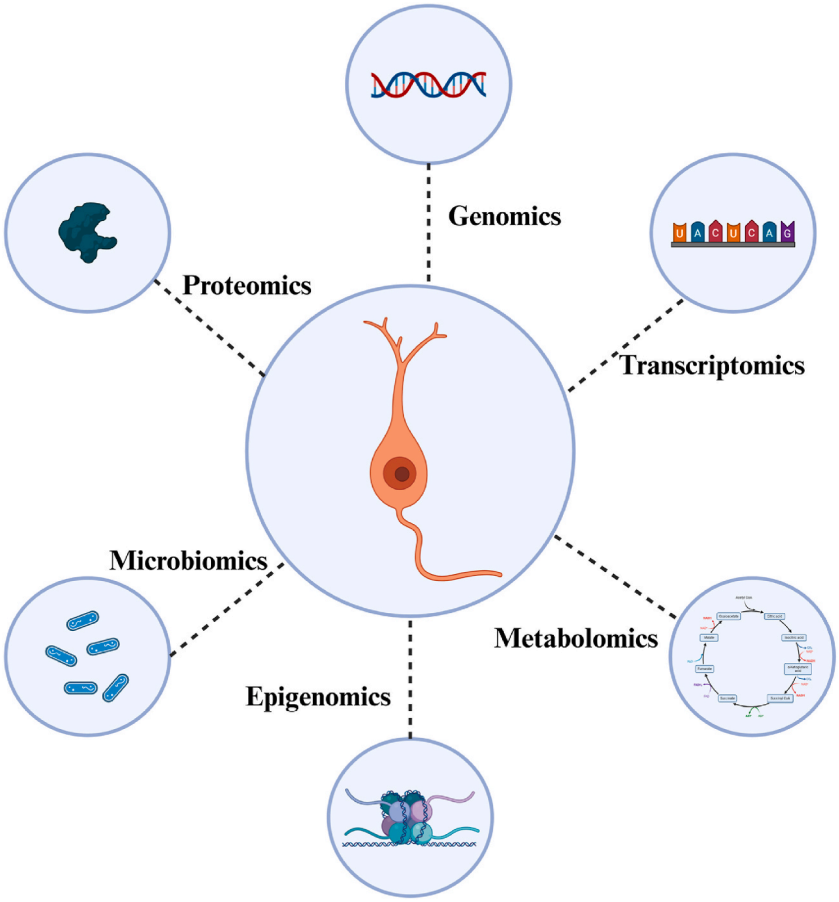


Fig. 3. Multi-omics studies of adult neurogenesis, including genomics, transcriptomics, proteomics, metabolomics, microbiomics, and epigenomics.

Table 1
Literature search on adult neurogenesis and multi-omics.

Search Strategy	Number of Papers
"Adult Neurogenesis" and "Genomics"	1091
"Adult Neurogenesis" and "Transcriptomics"	611
"Adult Neurogenesis" and "Proteomics"	160
"Adult Neurogenesis" and "Metabolomics"	38
"Adult Neurogenesis" and "Microbiomics"	93
"Adult Neurogenesis" and "Epigenomics"	47

proliferation, neuronal differentiation, synaptic plasticity, and neurodevelopment. Mutations in some of these genes can lead to deficits in neurogenesis, affecting cognitive and behavioral functions. Future research is essential to further investigate the functions and mechanisms of these genes and to explore new therapeutic approaches to promote neurogenesis and improve the treatment of neurodegenerative diseases.

2.2. Epigenomics

Epigenetic mechanisms are crucial dynamic processes for the regulation of various genome functions and coordination of brain development and adult neurogenesis [43]. The epigenetic pattern of normal cells is influenced by their age and (micro)environmental conditions. By combining these factors, a cell's epigenome influences its phenotype; as a result, a cell's phenotype varies slightly over time [44]. Major studies are summarized in Table 3.

DNA methylation, a highly researched area in adult neurogenesis epigenomics today, can regulate gene expression [45]. Age can seriously influence DNA methylation status, which presumably affects adult neurogenesis [46]. Mario Baumgart et al. studied the animal model of the short-lived teleost fish *Nothobranchius furzeri* [47]. The brains of scleractinian fish show extensive adult neurogenesis and neuronal regeneration. Compared with human data, several DNA methyltransferase gene family members were

Table 2
Main findings in genomics of adult neurogenesis.

Year published	Genes studied	Main findings	Biological material	Organism	Method used	References
2013	*Sox11 & Sox4*	Knockdown of both *Sox11* and *Sox4* significantly inhibited adult hippocampal neurogenesis	NPCs	Human	Retroviral method	[35,36]
2014	*SRD5A3*	The most likely mutation in cerebellar ataxia is the pure mutation c.5G > A (p.W19X) in exon 1 of *SRD5A3*	Cerebellum	Human	Exome sequencing analysis	[23,35]
2015	*SRRM4*	A reduction in Pax6+ cells and post-mitotic NeuN + neurons was observed in the ventricular zone of the *SRRM4*-deficient germline.	Brain	Human	CRISPR/Cas9	[20]
2016	*SRD5A3*	The presence of a purely nonsense mutation c.3G > A in the *SRD5A3* gene; p.Trp107X (chr4: g.5G > A [hg19])	Cerebellum	Human	Sanger sequencing	[23,37]
2016	*PMM2*	A compound heterozygous mouse model with the prevalent R137H and F115L mutations in *PMM2* showed neurodevelopmental defects similar to those in *PMM2*-CDG patients.	Cerebellum	Mouse	Knock-in technology	[24,37]
2016	*CSTB*	Reported 2 PME patients with a homozygous p.Arg68* null mutation	Cerebellum	Human	Single nucleotide polymorphism arrays	[24,30]
2017	*PMM2*	Forty-six different pathogenic variants of *PMM2* were identified, with the Arg141His variant being the most common	Cerebellum	Human	cDNA sequencing	[30,38]
2018	*Gas1*	Gas1 plays a role in neurodevelopment, with its expression regulated by NeuroD1	Cortex	Mice	Knock-in technology	[27]
2019	*AUTS2*	Abnormal number and density of cells in the hippocampal dentate gyrus and Ammon's horn of 16Gso pure mice	Hippocampal dentate gyrus and Ammon's horn	Mice	Hybrid selection and deep sequencing	[38,39]
2020	*CSTB*	The total number of proliferating cells was significantly reduced in p.Arg68* null mutation hCOs	hCOs	Human	Cell Culture	[39,40]
2020	*DIAPH3*	*DIAPH3* is essential for filopodia formation, which is required for neocortical neuropil development	Cortex	Human	cDNA sequencing	[31]
2020	*Sxt1a*	*Sxt1a* has a long-term impact on synaptic plasticity	Cerebellum	Human	cDNA sequencing	[29]
2022	*PTBP1*	Deletion of *PTBP1* may induce premature differentiation of radial glial cells into neurons, depleting the radial glial cell pool.	Brain	Human	CRISPR/Cas9	[25]
2024	*Tdrd3*	Specific knockout of *Tdrd3* enhances neuronal complexity and reduces myelin sheath formation in mice	Cerebellum	Mice	CRISPR/Cas9	[41]
2024	*Derlin-1*	Adult neurogenesis defects occur in neural stem cells lacking *Derlin-1*	Brain	Mice	CRISPR/Cas9	[33]
2024	*Hdac8*	The proliferation and differentiation of neural progenitor cells (NPCs) were found to be inhibited in *Hdac8*-specific knockout cells	Brain	Human	CRISPR/Cas9	[34]
2024	*Snhg11*	By knocking out the *Snhg11* in the wild-type mouse DG, it was found that synaptic plasticity and adult neurogenesis were impaired.	Dentate Gyrus	Mice	Cre-LoxP	[42]

downregulated during fish brain aging, revealed the authors' analysis. Post-translational epigenetic modifications occur in mouse dentate gyrus neurons with age. H3K9 trimethylation (H3K9me3) decreases during aging [48], but this decrease can be prevented by the cyclic induction of the Yamanaka factor used for cell reprogramming, Alberto et al. reported [49]. In vivo transient cyclic reprogramming in the central nervous system (CNS) may be successful for slowing down CNS aging and neurodegenerative disorders, the authors suggested.

Age also significantly affects cytosine 5 methylation within CpG dinucleotides. A weighted correlation network analysis of 2442 Illumina DNA methylation arrays from human brain and blood tissues performed by Steve Horvath et al. allowed the identification of age-related co-methylation modules [50]. The findings show that age affects adult neurogenesis, which is influenced in part by DNA methylation, and that the aging-related common module includes genes involved in nervous system development, neuronal differentiation, and neurogenesis. Using genome-wide DNA methylation sequencing, Zocher et al. found in 2021 that exposure to a stimulus-enriched environment counteracts age-related DNA methylation changes in the hippocampal dentate gyrus of mice [51]. Specifically, environmental enrichment prevents aging-induced CpG hypomethylation at target sites of the methyl-CpG-binding protein Mecp2, which is essential for neuronal activity and affects cognitive function, adult hippocampal neurogenesis, and other aspects.

Adult neurogenesis is controlled by cell-intrinsic molecular processes and behavioral activity. While de novo DNA methylation is essential for embryonic brain development, its role in adult hippocampal neurogenesis remains unknown. De novo DNA methyltransferase targets neuronal enhancers and gene bodies during the differentiation of adult hippocampal neural stem cells to establish the neuronal methylationome and promote transcriptional upregulation of neuronal genes, found Zocher et al. [52]. During in vitro

Table 3
Main findings in epigenomics of adult neurogenesis.

Year published	Location	Model organism	Main findings of Research	Method used	References
2012	Blood and brain tissue	Human DNA methylation data sets	The consensus module of DNA methylation associated with aging contains genes involved in nervous system development, neuronal differentiation and neurogenesis.	The standard protocol of Illumina methylation assays	[50]
2020	The dentate gyrus (DG)	Reprogrammable i4F-B mice (10 months age)	Markers related to adult neurogenesis decrease with mouse age.	qRT-PCR	[49]
2021	The cerebral cortex (CTX) and cerebellum (CB)	Transgenic heterozygous TgN $(hGFAP\text{-}EGFP)_{GFEA}$ and TgN$(PLP\text{-}DsRed1)_{PRDB}$ (PLP-DsRed1) mice (6-week-old)	The overall chromatin structure and in particular the number of open chromatin sites are remarkably distinct between astrocytes of the CB and CTX.	The R package methylKit	[56]
2021	The dentate gyrus (DG)	Female C57BL/6JRj mice (5 weeks old)	De novo DNA methylation is not needed for adult neural stem cell proliferation and fate determination, but for morphological and functional maturation of adult-born neurons in the hippocampus.	Sorted Binary Alignment Map files with the function processBismarkAln	[52]

differentiation of adult hippocampal neural precursor cells (NPCs) into neurons, focal DNA methylation changes may inhibit dendritic growth and synaptogenesis in developing neurons and hinder their functional maturation.

DNA demethylation also is important for adult neurogenesis in the hippocampus. For example, Gadd45b promotes DNA demethylation and alleviates the repression of genes essential for adult neurogenesis [53]. As for microRNAs, miR-9, miR-124, miR-92b, and miR-23 are selectively expressed at different stages of neural stem cell and progenitor cell lineage progression [54]. In adult neurogenesis, miR-9 inhibits NSC proliferation and promotes neural differentiation [55].

2.3. Transcriptomics

Transcriptomics is the study of the abundance of different types of RNA molecules to identify and analyze biological processes, signaling pathways, and potential biomarkers.

To determine the mechanisms of neurodegeneration, the HD iPSC Consortium [57] conducted RNA-seq analysis on induced pluripotent stem cells derived from patients with Huntington's disease (HD), revealing that gene expression in HD cultures was reduced in glutamate, GABA signaling, axon guidance, and calcium inward flow, with one-third of the gene changes occurring in pathways that regulate neuronal development and maturation [58]. Whether there is sustained neuronal neogenesis in the human olfactory bulb remains unclear. A microarray RNA quantitation analysis by Jörn et al. [59] of five adult olfactory bulbs revealed 669 overexpressed genes. Meanwhile, to explore further the biological functions covered by the expressed genes in adult olfactory bulbs, 94 meaningful GO terms were identified, including 48 gene ontology terms and 27 neuron development terms related to neurogenesis. Of the genes expressed in the adult olfactory bulb, one-fifth were associated with neuronal development, and half these genes were functionally associated with axon generation. However, the study has some shortcomings, and one possible confounding factor is that it is not impossible that growth factors reached these bulbs and stimulated neurogenetic processes during surgery, even though tumor invasion was ruled out at the histological level.

Previous studies have identified smaller hippocampal volumes in patients with psychiatric disorders and lower levels of hippocampal neurogenesis as possible causes [60]. Powell et al. [61] used human hippocampal progenitor cells for the first time to observe genome-wide expression during hippocampal differentiation. Microarray analysis uncovered extensive transcriptional reprogramming during neural progenitor differentiation, and gene ontology revealed the downregulation of genes controlling mitotic processes and upregulation of genes controlling cell differentiation. While the use of antiretroviral therapy (ART) has greatly decreased the morbidity and mortality of HIV-1 infection, HIV-1-associated neurocognitive disorders (HAND) remain prevalent [62]. Borjabad et al. found that neurogenesis-related genes were downregulated in brain cells of the anterior frontal lobe of HIV-1 patients [63].

Exome sequencing has recently identified causal mutations in 16 %–31 % of patients with intellectual disability (ID), but the noncoding regions of the human genome still have not been explored in greater depth [64]. To identify long noncoding RNAs (lncRNAs) associated with neurogenesis, D'haene et al. [65] pinpointed 53 candidate lncRNA genes, and Gene Set Enrichment Analysis showed that at least 24 lncRNAs are involved in processes such as synaptic transmission, nervous system development, and neurogenesis. Zinc finger protein and the structural domain containing 16 BTBs (Zbtb16) play important roles in neural precursor cell proliferation and neural differentiation [66], but how Zbtb16 influences brain function and behavior is still unclear. Usui et al. [67] identified 533 differentially expressed genes (DEGs) and found that Zbtb16 plays an important role in the neurogenesis of the deep layers and oligodendrogenesis. The above studies provide insights at the transcriptional level into the downregulation of neurogenesis-related genes due to HIV-1 infection and psychiatric disorders, as well as the roles of long-stranded noncoding RNAs and Zbtb16 in neurogenesis and cognitive function.

Growth arrest-specific 1 (Gas1) is a protein that attaches to cell membranes via glycosylphosphatidylinositol (GPI) anchor points. Previous studies have suggested that Gas1 plays a regulatory role in signaling during central nervous system development [68].

Estudillo et al. [26] demonstrated that Gas1 affects neural progenitors of the human developing cortex and the dentate gyrus of the hippocampus, and Quezada-Ramírez et al. [27] identified two highly conserved E-boxes in the human Gas1 promoter, which mediated the transcriptional upregulation of Gas1 by NeuroD1. Gas1 and NeuroD1 are jointly localized in the neocortex, the dentate gyrus of the hippocampus, and the external granular layer of the cerebellum, further studies revealed, and Gas1 is the direct target of NeuroD1. The apolipoprotein E4 gene allele and the apolipoprotein E4 protein (ApoE4) are risk factors for Alzheimer's disease [69]. To explore the effects of ApoE3 and ApoE4 heterodimers on adult neurons at the level of neurogenesis, Geffin et al. [70] investigated the human neural progenitor cell line hNP1 with genotype APOE3/3. Gene ontology found 41 genes to be downregulated and five of the top 10 GO terms to be associated with neurogenesis.

Bisphenol A (BPA), an endocrine-disrupting compound detected in more than 92 % of human urine samples, affects gene expression during fetal brain development [28]. To determine whether any DEGs are consistently expressed into adulthood, Henriksen et al. [29] showed that syntaxin 1a (Sxt1a), a gene that helps to regulate hormone and neurotransmitter release [71], was upregulated in the BPA-exposed mouse group, suggesting a long-term disruptive effect of BPA on synaptic plasticity. Bu-yang Huan-wu decoction (BHD) is a well-known herbal formula used to treat stroke in Asian countries such as China. To investigate its neuroprotective mechanism, Wang et al. [72] showed that BHD significantly upregulated six genes related to neurogenesis and nine genes related to nervous system development in mouse. These studies explored the effects of Gas1, ApoE4, BPA and BHD on neurogenesis and brain development, providing scientific evidence at the transcriptional level for a deeper understanding of the mechanisms of neurogenesis and brain development.

Recently, single-cell RNA sequencing has been widely applied to the process of adult neurogenesis, particularly the differentiation of neural stem cells (NSCs) in the adult brain. Hochgerner et al. [73] used scRNA-seq to map the transcriptional landscape of the adult hip-pocampus, identifying distinct neural progenitor cell populations and their differentiation into granule neurons. Their work highlighted the presence of neural intermediate precursor cells (NIPCs), which are essential for adult hippocampal neurogenesis. This study provides critical insights into the molecular mechanisms underlying adult neurogenesis, specifically the regu-latory pathways governing the differentiation of NSCs into mature neurons. At the cortical level, Marcy et al. [74] demonstrated that the neural stem cells in these areas can remain quiescent or activated depending on local microenvironmental signals. In the dentate gyrus, the quiescence of NSCs is regulated by intrinsic and extrinsic factors, including bone morphogenetic proteins (BMPs), which control the balance between stem cell dormancy and proliferation. The activa-tion of these NSCs and their differentiation into granule cells is a fundamental process in the adult brain's capacity for learning and memory formation.

Regarding cortical developmental mapping, Di Bella et al. [75] used single-cell RNA sequencing to analyze chromatin in the mouse cortex to develop a comprehensive map of mouse cortical development. Ziffra et al. [76] performed scATAC-seq on the human forebrain and showed the diversity among cortical neural progenitors. Herring et al. [77] analyzed gene expression and chromatin accessibility in the human prefrontal cortex from gestation to adulthood and revealed the dynamic regulatory landscape of human cortical development. Magrinelli et al. [78] used FlashTag to fate-map simultaneously born cohorts of AP daughter neurons at successive stages of corticogenesis. Eze et al. [79] used spatial transcriptomics to further delineate a comprehensive molecular and spatial map of the human cerebral cortex at early stages of development. These studies lay the foundation for diverse regulation of cortical cells.

While meaningful research has been conducted in some brain regions, it still needs more depth. Aldinger et al. [80] used laser capture microscopy and SPLiT-seq single-nucleus transcriptomics to map the human fetal cerebellum's molecular, cellular, and spatial composition, laying the cytological foundation for cerebellar neuron development. Peng et al. [81] performed single-cell RNA sequencing of 1741 neurons from multiple brain regions in mice and identified 11 subtypes, each with a wide range of projection diversity. Kim et al. [82] used the same method to analyze the hypothalamus of the chick at various stages of development. They identified many candidate neurogenic regulators that had not been identified before. Lust et al. [83] analyzed cell populations in the telencephalon of the salamander during regeneration, revealing the transcriptional dynamics and gene regulation of specific neurogenesis in the postembryonic region. Srivatsan et al. [84] used spatial transcriptomics to capture the approximate spatial coordinates and complete transcriptomes of approximately 120,000 mouse nucleus. The fate of neural stem cells is altered by Traumatic Brain Injury, promoting neurogenesis at the expense of astrocyte generation, as revealed by single-cell RNA sequencing and spatial transcriptomics [85]. Thousands of genes exhibiting anatomical expression patterns were identified, further refining mammalian development's spatially resolved single-cell map. Zhou et al. [9] revealed many immature dentate granule cells in the adult hippocampus, where low-frequency de novo neogenesis and prolonged maturation processes give the hippocampus its neurogenic capacity. The above studies cover multiple brain regions at the spatial transcriptomic level, including fetal cerebellum, mouse and avian hypothalamus, salamander brain cells, and mammalian developmental single-cell lineage maps, which provide valuable scientific data for a deeper understanding of brain development, and help to reveal the key factors of neurogenesis and the potential targets for treating related disorders.

At the progenitor cell level, Shi et al. [86] used single-cell RNA sequencing to study the diversity of human ganglionic eminences, identifying regional and temporal diversity among progenitors. Bocchi et al. [87] performed 96,789 single cells from the early human fetal striatum for Single-cell transcriptional analysis, which showed that D1 and D2 medium spiny neurons originated from the same progenitor cells and exhibited a continuum of fate determinants. Much research has also been carried out on single neuron de novo neuronization mechanisms. Bajaj et al. [88] investigated the migration of human intermediate neurons and its comprehensive quantitative analysis of functional regulation through neurotransmitter signaling. The results showed that neurotransmitter signaling pathways such as GABA link interneuron migration to maturation. Fu et al. [89] enriched and characterized various glial cells and neuronal progenitors of the neuronal lineage by single-cell RNA sequencing of EGFR-positive glial cells. Fiorenzano et al. [90] established the developmental trajectory from pluripotent stem cells to mature dopamine neurons using single-cell RNA sequencing.

Table 4
Main findings in transcriptomics of adult neurogenesis.

Year published	Transcript studied	Main findings	Biological material	Organism	Method used	References
2021	*Sxt1a*	Syntaxin 1a expression was upregulated in the BPA-exposed group, indicating long-term disruption of synaptic plasticity by BPA.	Mouse	Hypothalamus	RNA sequencing, RT-qPCR	[67]
2021	Genes in human fetal cerebellum	Mapping the molecular, cellular and spatial composition of the human fetal cerebellum	Human	Cerebellum	Laser capture microscopy and SPLiT-seq single-nucleus transcriptomics	[80]
2021	Genes in mice cortex	Revealing the developmental and differentiation processes of neuronal subtypes	Mice	Cerebral Cortex	Single-Cell Analysis	[92]
2021	Genes in human interneurons	Neurotransmitter signaling pathways such as GABA link interneuron migration to maturation	Human	Brain	Single-Cell Analysis	[88]
2021	Genes in human brain	Differentiation of cortical regions is driven by a strong gradient formed by frontal and occipital gene-expression signatures	Human	Brain	Single-Cell Analysis	[93]
2021	Genes in fetus brain	D1 and D2 medium spiny neurons originated from the same progenitor cells and exhibited a continuum of fate determinants.	Human	Brain	Single-Cell Analysis	[87]
2021	Genes in mice cortex	Producing a comprehensive map of mouse cortical development	Mice	Cerebral Cortex	Single-Cell Analysis	[75]
2021	Genes in human cerebral cortex	Depicting a comprehensive molecular and spatial map of the human cerebral cortex at early stages of development	Human	Cerebral Cortex	Single-Cell Analysis	[79]
2021	Genes in human brain	Establishing a developmental trajectory from pluripotent stem cells to mature dopamine neurons	Human	Brain	Single-Cell Analysis	[90]
2021	Genes in human cerebral cortex	Enriching and characterizing various glial cells and neuronal lineage progenitors	Human	Cerebral cortex	Single-Cell Analysis	[89]
2021	Genes in human brain	Identifying 11 isoforms (CTX1-11) and finding a wide range of projection diversity in each isoform	Mice	Brain	Single-Cell Analysis	[81]
2021	Genes in human brain	Identifying regional and temporal diversity among progenitor cells	Human	Brain	Single-Cell Analysis	[86]
2021	Genes in human brain	Discovering diversity among cortical neural progenitor cells	Human	Brain	Single-Cell Analysis	[76]
2021	Genes in human brain	Analyzing gene expression and chromatin accessibility in the human prefrontal cortex from gestation to adulthood	Human	Cerebral cortex	Single-Cell Analysis	[77]
2022	Genes in Chick hypothalamus	Identifying a number of previously unrecognized candidate regulators associated with neurogenesis	Chick	Hypothalamus	Single-Cell Analysis	[82]
2022	Genes in Salamander telencephalon	Unraveling the transcriptional dynamics and gene regulation of specific neurogenesis in the posterior region of the salamander embryo	Salamander	Telencephalon	Single-Cell Analysis	[83]
2022	Genes in human cerebral cortex	Employing FlashTag technology to track and determine the developmental fate of cohorts of AP daughter neurons	Human	Cerebral Cortex	FlashTag	[78]
2022	Genes in mice spinal cord	Revealing the regulatory role of histone H3-lysine 27 demethylase Kdm6b in the neogenesis of mouse spinal cord motor neurons	Mice	Spinal cord	Single-Cell Analysis	[91]
2022	Genes in human hippocampus	Revealing the presence of a large number of Immature dentate granule cells in the adult hippocampus	Human	Hippocampus	Single-Cell Analysis	[9]
2023	Genes in human cerebral cortex	Bone morphogenetic protein plays a key role in pallial germinal activity	Human	Cerebral Cortex	Single-Cell Analysis	[74]
2024	Genes in human hippocampus	The fate of neural stem cells is altered by Traumatic Brain Injury, promoting neurogenesis at the expense of astrocyte generation	Human	Hippocampus	Single-Cell Analysis	[85]

Table 5
Main findings in proteomics of adult neurogenesis.

Year published	Location	Model organism	Main findings of Research	Method used	References
2004	Cerebral cortex	15 day Charles River CD1 mouse embryos	Stathmin played an important role for in the migration of newborn neurons in the adult brain.	Two-dimensional differential in-gel electrophoresis and mass spectroscopy	[97]
2015	Hippocampus	6–8 week-old male Male C57BL/6j mice (6–8 week-old)	Comparative proteomics between saline (SAL)- and KA-treated animals identified a total of 2327 proteins in the DG, with 56 up- and 58 down-regulated in the KA group	LC–MS analysis	[113]
2015	Hippocampus	Dorfin$^{-/-}$ mice (4 and 8 weeks)	There are 24 proteins whose ubiquitination levels were substantially decreased (>2.5 fold) in the Dorfin−/− brain relative to WT controls.	Liquid chromatography-tandem mass spectrometric (LC-MS/MS) analyses	[102]
2016	Hippocampus	Female and male C57BL/6 mice (10 days or 10 weeks old)	Only a subset of 11 proteins was shared between 10D- and 10W-irradiated mice (Cct4, Caskin1, Hspd1, Tmod2, Prrt2, Uba1, Nptn, SOD1, Pdxp, Rab7 and Rac1), 3 of which showed deregulation of the same direction (Hspd1, upregulated; Pdxp and Rac1, downregulated)	Tandem mass spectrometry	[101]
2017	Dentate gyrus; cerebrospinal fluid	Human neural progenitor; Young adult Mice (C57BL/6 N from Charles River Laboratories, France) between 8 and 10 weeks of age	The expression of neural progenitor markers, such as Sox2 and Nestin, decreased as the cells matured, whereas the expression of markers of immature neurons, including Dcx, NCAM1, Gpr56, Tubb3 and Elav3, increased over time.	Mass spectrometry analysis	[98]
2020	Sub-ependymal zone (SEZ), Cerebral cortex (Cx) gray matter (GM), medial sub-ependymal zone (MEZ) and olfactory bulb (OB)	Male C57BL/6J mice between 8 and 10 weeks	4786 proteins had a differential abundance among the four regions: the Cerebral cortex (Cx) gray matter (GM), the OB, the SEZ, and the MEZ.	Mass Spectrometric Data Analysis	[99]
2020	Hippocampus	Patients with refractory MTLE	Bioinformatics analyses revealed upregulated proteins in dispersed samples were involved in developmental cellular migratory processes.	MSe label-free quantitative proteomics	[114]
2021	Hypothalamus	Human Brain	There is an enrichment of proteins pertaining to autophagy and adult neurogenesis in the proteome data.	High-resolution mass spectrometry approach	[104]
2021	Cerebrospinal fluid	Adult humans (*Homo sapiens*); mice (*Mus musculus*); sheep (*Ovis aries*); chickens (Gallus gallus); budgerigar (*Melopsittacus undulatus*) and cockatiel (*Nymphicus hollandicus*).	Comparative pathways analyses of CSF and blood plasma indicated clusters of proteins involved in neurogenesis, neural development and neural differentiation overrepresented in CSF in each species.	Liquid chromatography-tandem mass spectrometry (nLC-MS/MS)	[112]
2022	Hippocampus	human brain	The topline findings on age-associated proteome changes include altered expression of proteins associated with adult neurogenesis with age in the dentate gyrus.	Tandem mass tag-based high-resolution mass spectrometry	[103]
2022	Brain tissues	TG6799 mice	Despite significant difference in overall phosphoproteome profiles, molecular signatures and biological pathways have something in common between two insulin-resistant conditions.	Electrospray ionization (ESI)–tandem mass spectrometry (MS/MS)	[96]

Wang et al. [91] discovered the regulatory role of histone H3-lysine 27 demethylase Kdm6b in the neogenesis of mouse spinal cord motor neurons. More related studies are listed in Table 4.

2.4. Proteomics

Proteins are intimately involved in the execution and control of nearly all cellular processes. The proteome refers to a collection of proteins expressed in a particular environment at a particular moment. Methods for identifying, quantifying, and visualizing these proteins are referred to as "proteomics" [94]. One of the most important future proteomics developments will be the generation and dissemination of big proteomic datasets with the potential to inspire new computational techniques, such as deep learning-based algorithms [95]. Related studies are summarized in Table 5.

The kind and quantity of proteins in tissues connected to adult neurogenesis are influenced by disease conditions. It is well known that insulin in the brain influences mature neurogenesis in the hippocampus. Insulin receptor substrate 2 (Irs2) phosphorylation typically was elevated in both insulin resistance conditions (induced by either TNF-α or palmitate), Dayea Kim et al. discovered in 2022 using a phosphorylation proteomics method in Neuro-2a (N2a) cells [96]. Both insulin resistance conditions led to an increase in sequestosome-1 phosphorylation and a typical decline in the phosphorylation of insulin receptor substrate 2 (Irs2). However, the interacting proteins between the two groups and the pathway analysis between the two separate phosphorylated proteomes were different, implying that insulin intolerance can result in distinct phosphorylation patterns.

Using two-dimensional difference gel electrophoresis (2D DIGE) to isolate and compare proteins expressed in immature and mature cultures of embryonic rat cerebral cortexes in 2004, Jin et al. identified 1033 protein spots. Adult rodent brains had significant stathmin expression in the neuroproliferative zone and neuronal migration pathways, research showed. Stathmin is a developmentally regulated cytoplasmic protein expressed at high levels in the brain, which is involved in new neuron migration in the mature brain [97]. After the start of neuronal differentiation, a discovery proteomics screen of neural progenitor cells (hNPCs) derived from human embryonic stem cells (hESCs) at various developmental phases showed that 4400 proteins were dynamically expressed during differentiation, Lugert et al. found. The expression of immature neuronal markers such as Dcx, NCAM1, Gpr56, Tubb3, and Elav3 increased over time, and the expression of neural progenitor cell markers such as Sox2 and Nestin declined as cells developed. Proteoglycan Glypican-2 (Gpc2)'s extracellular release raises the possibility that it could be used as a marker to track adult neurogenesis [98].

Researchers have performed proteomic analyses of different cells and tissues. In 2020, Kjell et al. identified proteins from the subependymal zone (SEZ), cerebral cortex (Cx) gray matter (GM), medial subependymal zone (MEZ), and olfactory bulb (OB). In a principal component analysis (PCA) of the four regions, the OB had a greater proportion of gene regulatory proteins, probably because of the large number of mature adult neuronal cells, and less evident synapse-related features and core matrix proteins. The membrane-associated protein family is more prevalent in the SEZ, whereas proteoglycans involved in neuronal development and migration are concentrated in the OB, potentially linking them to neuron-forming cells in this area. These proteomic results confirm the regional nature of adult neurogenesis, arguing for a role of molecules such as transglutaminase 2 (Tgm2) in neuronal integration and prominence generation [99]. Deletion of Scaffold attachment factor B (SAFB) increases oligodendrocyte formation in the adult hippocampus and selectively regulates neural stem cells [100].

Casciati et al. used tandem mass spectrometry to measure total protein alterations in the hippocampus six months after exposing 10-day-old and 10-week-old mice to 2 Gy of x-ray radiation. Only 11 proteins were shared by the two age groups of irradiated mice, as were three significantly altered signaling pathways, including oxidative phosphorylation and superoxide radical degradation. The signaling pathway endothelial adhesion junction remodeling, however, was substantially changed only in the younger age group. These findings imply that the timing of therapeutic radiation exposure can significantly influence adult neurogenesis, radiation vulnerability is strongly influenced by age, and younger children are more susceptible to cognitive decline than adults [101].

Protein ubiquitination has important implications for various aspects of neuronal development and function. Dorfin, also known as Rnf19a, is a RING finger E3 ubiquitin ligase. Dorfin mutant (Dorfin −/−) mice exhibit reduced adult neurogenesis in the hippocampal dentate gyrus and impaired contextual fear-conditioning reflexes, Park et al. reported, finding 24 proteins with reduced ubiquitination, including Gsn, Rab11b, and other proteins. These findings imply that adult neurogenesis, synaptic plasticity, and contextual fear memory may be regulated by Dorfin and that Dorfin deficiency in rodents causes decreased neurogenesis in the DG [102].

When hippocampal tissues from 12 people belonging to four different age groups were subjected to a proteomic analysis in 2022, Praseeda Mol et al. discovered that lysosomal and oxidative phosphorylation were enriched in the 81- to 90-year-old age group while other processes, like nervous system development, synaptic plasticity and transmission, and messenger RNA (mRNA) splicing, were more prevalent in the younger age groups [103]. In 2021, Chatterjee et al. performed a proteomic analysis of the adult hypothalamus and identified proteins of high abundance, such as proteolipid protein (PLP1), myelin basic protein (MBP), and tubulin (Tubb), and the 10 % most abundant proteins were associated with cytoskeleton organization, cellular metabolic process regulation, myelin formation, and mitochondrial function [104]. There may be a neurogenic ecological niche in the hypothalamic region [103]. Experiments with neural stem cells isolated from the adult rat hypothalamus laid the foundation for understanding adult mammalian hypothalamic neurogenesis [105]. Studies have identified neuronal stem cell markers, such as nestin (NES), vimentin (VIM), notch receptor 2 (NOTCH2), and CD63,and differentiated neuronal and astrocytic markers, like internexin neuronal intermediate filament protein alpha (INA), MAP2 tubulin beta 3 (Tubb3), neurofilament light chain (NEFL), and neurofilament medium chain (NEFM), which are consistent with earlier studies that pointed to the existence of new and differentiated neuronal assemblies in the adult hypothalamus [106,107]. Additionally, hypothalamic neurogenesis contributes to neuroprotection and anti-aging.

Adult neurogenesis is coordinated by the rigorous regulation of intrinsic and extrinsic factors. Cerebrospinal fluid (CSF) fosters,

maintains, and supports the growth of neurogenic ecotopes [108,109] and can promote neurogenesis in neural stem cells [110]. Voukali et al. gathered cerebrospinal fluid samples from people, mice, sheep, and birds for proteomic research. According to an enrichment analysis, the most statistically significant and frequent terms across all species and datasets were related to neurogenesis, nervous system development, axonal development, neuronal projection development, and cell migration. Characterization of gene ontology (GO) biological processes also revealed 71 rich pathways, including cellular component assembly, cell morphogenesis regulation, developmental cell growth, and synaptic signaling. In this neighborhood, there are still a lot of unanswered issues. The underlying mechanisms of adult neurogenesis will be explored in cerebrospinal fluid comparative proteomic studies, and this research will eventually be translated into regenerative interventions [111,112].

2.5. Metabolomics

Metabolomics (also spelled metabonomics; the two terms are frequently used interchangeably) describes the comprehensive analysis of metabolites (small molecules with molecular weights less than 1500 Da) and other exogenous and endogenous chemicals in biological specimens and their responses to various perturbations or interventions [115]. Additionally, metabolomics' intrinsic ability to identify minute changes in biological pathways makes it possible to understand the mechanisms underlying a wide range of physiological conditions and abnormal processes [116].

There are many studies on adult neurogenesis conducted in animal models. In 2013, Angelo D'Alessandro et al. discovered that a transcription factor belonging to the p53 family, trans-activated (TA) p73, can regulate a variety of biological processes, including neurogenesis, differentiation, and apoptosis. In metabolomic studies, TAp73α increased arginine-citrulline-NO metabolism and

Table 6
Major findings in metabolomics of adult neurogenesis.

Year published	Location	Model organism	Main findings of Research	Method used	References
2013	N/A	The human osteosarcoma SAOS-2 cell line	Expression of TAp73α increased rates of Krebs metabolism	Targeted Metabolobomics and Lipidomics (Multiple Reaction Monitoring)	[117]
2014	Hippocampus	Mouse model for single dose 8 Gy cranial irradiation (8–10 weeks old)	Metabolic activity in the hippocampus of mice subjected to cranial irradiation generally decreased.	^{1}H NMR spectroscopic and PCA analysis	[124]
2015	Brain tissues (mainly consisting of striatum, cortex, RMS, SVZ, and Hippocampus)	TRIM32 knockout mice (65 (±2) days of age)	The concentration of 3-phosphoglyceric acid, was significantly higher in the tissue of TRIM32 ko mice	GC-MS analysis	[119]
2019	Striatum, hippocampus, and OB	Adult male Wistar rats (3–4 months old)	Evaluation of brain metabolites after irradiation performed showed a significant decrease in the total N-acetylaspartate to total creatine (tNAA/tCr) ratio in the striatum, hippocampus, and OB.	Proton nuclear magnetic resonance (1H NMR)-based metabolomics and proton magnetic resonance spectroscopy (1HMRS)	[118]
2019	N/A	Neuro2a cells	Nine metabolites such as arginine, aspartate, glutamine, glyceraldehyde-3-phosphate/dihydroxyacetone phosphate, phosphoenolpyruvate, pyruvate, ribulose/xylulose/ribose-5-phosphate, fumarate, and malate were decreased in N2a EtBr-treated cells.	Liquid chromatography/tandem mass spectrometry (LC-MS/MS) method	[125]
2020	N/A	NT2-N cell	Psychoactive drugs showed the alterations in the levels of metabolites involved in neuronal health, particularly NAA and GABA	Gas chromatography–mass spectrometry (GC-MS) analysis	[120]
2022	Hippocampal tissue	Male ICR mice (4 weeks old)	EPs can manipulate the tryptophan metabolite as a novel preemptive therapy for neurodevelopmental disorders.	Widely targeted metabolomics and targeted metabolomics	[122]
2022	Brain tissue	APPswe/PS1ΔE9 transgenic (Tg) mice (9-month-old)	Broussonetia papyrifera (L.) L'Hér. ex Vent. fruits water extract (BLWE) could modulate endogenous metabolic compounds in the brains of AD mice, including N-acetyl-aspartate, glutamine, etc.	Ultimate 3000 liquid chromatograph (LC) combined with Q Exactive mass spectrometer (MS)	[123]
2022	Frozen stool samples	Wild-type or heterozygous mice lacking one Ptch1 allele (8 weeks of age)	Fecal metabolic profiles indicate increasing metabolic alterations with a reduced abundance of metabolites in chronic vs. acute colitis.	LC-ESI-MS analysis	[126]

promoted glutathione homeostasis [117]. According to the first metabolomics study applied in vitro (1)H NMR spectroscopy, which was conducted in 2014 by Poonam Rana et al., impaired neurogenesis was present within 24–48 h of radiation exposure, as evidenced by decreased metabolic activityand reduced glucose utilization in hippocampal tissue extracts. Using proton magnetic resonance spectroscopy (1) H MRS to show brain metabolites in rats 15 weeks after exposure to whole brain irradiation, Soňa Bálentová et al. found a significant decrease in the ratio of total N-acetylaspartate to total creatine (tNAA/tCr) in the striatum, hippocampus, and olfactory bulb (OB), indicating increased neurodegeneration and neurogenic inhibition [118].

Metabolomics has also demonstrated that, in addition to irradiation, a variety of molecules or substances affect metabolites linked to adult neurogenesis. For example, several metabolic intermediates connected to glycolysis, glycine, or cysteine metabolism are dysregulated at the molecular level in the brain tissue of *TRIM32* knockout animals, Hillje et al. found. These metabolomic pathways were shown to be directly or indirectly associated with impaired neurogenesis, anxiety, or depression-like behaviors [119]. Bortolasci et al. studied six drugs with neurogenesis effects on the levels of metabolites that are markers of neuronal maturation. Most of the evaluated metabolites were increased in NT2-N cells in the experimental group compared with controls, particularly N-acetyl-l-aspartate, l-glutamic acid, and gamma-aminobutyric acid, while metabolites like amisulpride, quetiapine, and glutathione were not elevated [120]. Lifestyle factors, like exercise, may also promote adult hippocampal neurogenesis [121].

Oral Eucommiae cortex polysaccharides (Eps) significantly inhibited the kynurenine (Kyn) pathway in mice fed an obesogenic diet (OD), as evidenced by reduced serum Kyn and Kyn/Trp ratios, thereby exerting potential neuroprotective effects and reducing OD-induced cognitive and social dysfunction, Sun et al. reported [122]. Broussonetia papyrifera (L.) L'Hér. Ex Vent. Fruits water extract (BLWE) could regulate endogenous metabolic compounds in the brains of mice with Alzheimer's disease, Yan et al. found, reporting that eight metabolites were increased in the experimental group. These findings demonstrate that BLWE could enhance neural stem cell proliferation and improve neurogenesis, effectively repairing damaged neurons in the hippocampus [123]. More related studies have been summarized in Table 6.

2.6. Microbiomics

Microbiomics is now becoming one of the key targets in adult neurogenesis research because it is susceptible to lifestyle and environmental influences. Studies of the gut microbiota and the gut-brain axis (GBA) have received increasing attention in recent years, with growing evidence showing that the gut microbiota is closely related to the proliferation and differentiation of neural stem cells and adult neurogenesis [127–129]. This relationship can be divided into the direct action of the gut microbiota and the action of gut microbiota on the biotransformation of natural dietary compounds such as polyphenols.

Bacterial cell wall peptidoglycan (CW) is a prevalent pathogen-associated molecular pattern (PAMP) for toll-like receptor 2 (TLR2), Jessica et al. [130] found, and CW can enter the developing fetal brain because of the permeability of the placental barrier, although fetal brains exposed to CW did not show any signs of inflammation or neuronal death. However, neurotranscription factor FoxG1 is induced and neuroproliferation is activated, eventually leading to a 50 % increase in neuronal density in the cortex and a potential impact on cognitive function later in life. Ait-Belgnaoui et al. [131] pretreated mice that were already in a state of chronic mental stress with a probiotic combination of *Lactobacillus* swiss R0052 and *Bifidobacterium longum* R0175. A quantitative analysis of doublecortin-positive cells showed that the probiotic inhibited the reduction of hippocampal neurogenesis and the downregulation of hypothalamic gene expression involved in synaptic plasticity.

Gut bacteria have an important regulatory and directive role in the developmental processes of CNS neurogenesis, especially in the hippocampal region, recent studies have shown [132]. By transplanting microflora from SL/vulnerable rats, which have more anxiety and depression-like behaviors, into the immature mouse gut, Jiah et al. [133] found that microglia density in the ventral hippocampus (vHPC) and IL-1β expression were increased, suggesting that the gut microbiome plays an important role in depressive behaviors as well as inflammatory responses in the vHPC of stressed individuals. Using bromodeoxyuridine to label proliferating cells in mice, Ebere et al. [134] found increased adult hippocampal neurogenesis in the dorsal hippocampal region of germ-free mice. However, microbial colonization of germ-free mice after weaning did not change adult hippocampal neurogenesis, suggesting the existence of a critical checkpoint in early life during which microbial colonization will affect adult hippocampal neurogenesis.

While the widespread use of antibiotics has saved millions of lives, it has also had many adverse effects [135]. According to previous studies, the overuse of antibiotics severely disrupts the mouse gut microbiome [136]. Mohle et al. [137] used NeuN to label mature neurons and doublecortin (DCX) to label neuronal progenitor cells (NPC) after the treatment of adult mice with broad-spectrum antibiotics, showing that both mature neurons and neuronal progenitor cells were significantly reduced in the antibiotics-treated group compared with the undrugged group. The results suggest that antibiotics inhibit hippocampal neurogenesis in adult mice by disrupting the gut microbiome. Probiotic *lactobacilli* are now used in a variety of foods and health care products [138] to regulate intestinal homeostasis and immunity. Heat-inactivated *Lactobacillus* brevis SBC8803 induces serotonin release from intestinal cells, which affects autonomic and sleep rhythms, previous studies have shown. However, the relationship between SBC8803 and cognitive function remains poorly investigated. In immunohistochemical studies of labeled proliferating cells in the hippocampal region of mice fed heat-inactivated SBC8803 chow, the number of proliferating cells was significantly higher in the SBC8803 group than in the control group, Rie et al. reported that SBC8803 may promote adult hippocampal neurogenesis [139]. In summary, these studies have explored neurodevelopment from both positive and negative perspectives of antibiotics and probiotics, and although there are still some unknowns, the findings provide important references for a deeper understanding of the mechanisms of the gut-brain axis and provide insights for the development of new therapeutic strategies.

Brain-derived neurotrophic factor (BDNF) plays a key role in several aspects of hippocampal neuronal plasticity and function by interfering with the gut-brain signal [140]. The intestinal microbiota influences the synthesis and release of BDNF. Based on this

knowledge, Olivia et al. [141] severed the vagus nerve in mice, finding that BDNF mRNA was downregulated in all regions of the hippocampus and that the proliferation and survival of newborn cells were decreased. The number of immature neurons with complex dendritic morphology was reduced more significantly. However, the study has shortcomings. For example, although the vagus nerve serves as an important communication channel between gut bacteria and the brain [142], the study could not exclude the effect of the vagus nerve itself on adult hippocampal neonates.

While previous studies have shown that the internal composition of the gut microbiome evolves as the host ages [143], the effect of microbial population evolution on adult neurogenesis is still unknown. When Parag et al. [144] transplanted the gut microbiome from old or young mice, respectively, into young germ-free mice, brain hippocampal neurogenesis was upregulated in the mice that received transplants from aged donor mice; further metagenomic analysis revealed an age-sensitive enrichment of butyrate-producing microbes in these transplanted mice. Elevated butyrate concentrations promoted an increase in fibroblast growth factor 21 (FGF21), which led to an elevation in AMPK and SIRT-1 activation and a reduction in mTOR signaling. The researchers replicated previous results using exogenous sodium butyrate treatment in young germ-free mice, suggesting that gut microbiota transplantation from an aged host can promote adult neurogenesis in young recipients. Chronic inflammation affects adult hippocampal neurogenesis, but azithromycin can counteract these effects by modulating the gut microbiota [145]. Disturbances in the microbiota also impact behaviors associated with

Table 7
Main findings in microbiome of adult neurogenesis.

Year published	Components of bacteria/ substrate	Main findings	Biological material	Organism	Method used	References
2013	Probiotics	Probiotics suppress the reduction of hippocampal neurogenesis and the downregulation of hypothalamic gene expression involved in synaptic plasticity	Mouse	Hippocampus and hypothalamus	Quantifying doublecortin-positive cells	[146]
2013	CJLJ103	CJLJ103 inhibits lipopolysaccharide-induced activation of nuclear factor-kB in the hippocampus and attenuates the inhibitory effect of lipopolysaccharide on brain-derived neurotrophic factor expression	Mouse	Hippocampus	Fecal transplants	[138]
2014	Cell wall peptidoglycan	Bacterial peptidoglycan crosses the placenta and activates toll-like receptor 2 (TLR2), leading to alterations in fetal neurodevelopment	Mouse	Cortex	Immunohistochemistry and immunofluorescence	[131]
2014	BDNF	When the vagus nerve was severed in mice, BDNF mRNA was down-regulated in all regions of the hippocampus	Mouse	Hippocampus	Immunohistochemistry and in situ Hybridization	[136]
2015	Lactobacillus	SBC8803 may promote adult hippocampal neurogenesis	Mouse	Hippocampus	BrdU Treatment	[134]
2016	Gut microbiota	The gut microbiome plays an important role in depressive behavior as well as in inflammatory responses in stressed individuals vHPC.	Mouse	Ventral hippocampus	Fecal transplants	[130]
2018	Bromo-deoxyuridine	There is a critical checkpoint in early life during which microbial colonization will affect adult hippocampal neurogenesis	Mouse	Hippocampus	Bromo-deoxyuridine label	[132]
2018	Polyphenol	Phenols can affect their own metabolism by altering the dominant populations in the gut. This leads to increased production of neurotransmitters such as 5-hydroxy-tryptamine in the hippocampus and striatum, which in turn promotes neuronal survival	Mouse	Hippocampus	Chromatographic (HPLC-ED) analyses	[147]
2020	Antibiotics	Antibiotics inhibit hippocampal neurogenesis in adult mice by disrupting intestinal flora	Mouse	Hippocampus	BrdU Treatment	[133]
2022	Butyrate	Transplantation of intestinal microbiota from older hosts can promote the generation of young recipient adult neurons	Mouse	Hippocampus	Metagenomic and immunofluorescence staining	[142]
2024	LPS	Chronic inflammation affects adult hippocampal neurogenesis, and the use of azithromycin can reverse these negative effects by modulating the gut microbiota	Mouse	Cortex	Hippocampal Cytokine Analysis	[145]
2024	Antibiotics	Disruption of the microbiota affects adult hippocampal neurogenesis-related behaviors, which can be alleviated by voluntary exercise	Mouse	Hippocampus	Metabolomics Analysis	[121]

adult hippocampal neurogenesis, which can be alleviated by voluntary exercise [121]. And other related studies are summarized in Table 7.

3. Conclusion and Perspective

Although many studies have explored adult neurogenesis at the molecular mechanistic and functional levels, these studies have some limitations. There is evidence that neurogenesis begins to slow down after birth and may cease during adolescence. Although we know that adult neurogenesis is downregulated with age, the exact mechanisms and timepoints remain unclear. In most animal models, adult neuronal markers take at least several months to be expressed, and adult neuronal onset may take even longer, creating more uncertainty about the use of postmortem brains for studies.

Adult neurogenesis is a potential treatment for many neurodegenerative diseases. Many studies are now being conducted on animal models. Factors discovered through multi-omics may be able to help stimulate neurogenesis in patients with neurodegenerative diseases for therapeutic purposes. However, there is still a lack of human trials due to ethical issues and lack of human brain specimens, slowing down the development of therapeutic drugs. Most genetic studies of adult neurogenesis have focused on genetic variation in candidate genes such as SRD5A3, PMM2, AUTS2, CSTB, PTBP1, NLGN4X, and Foxp1. However, most of the studies have only detected motif changes, and there have been few studies of polymorphisms. Epigenetic mechanisms control key processes of different genomic functions. In recent years, the epigenetic effects of adult neurogenesis have been extensively explored in animal models, but the specific role of adult neurogenesis and the molecular pathways involved have yet to be explored in greater depth.

Many studies have explored the mechanisms of adult neurogenesis by examining various biometabolic processes. However, most studies focus only on one part of biometabolism and rarely on its upstream and downstream processes, which is insufficient. A growing body of research suggests that gut microbes play key roles in adult neurogenesis either directly or indirectly through the gut-brain axis. However, most of the current studies are from animal models due to the inability to make prospective estimates in living humans. In addition, there is no real specific mechanistic link to demonstrate a direct role of gut microbes with adult neurogenesis.

From a translational medicine perspective, adult neurogenesis presents significant potential for the treatment of neurodegenerative diseases. Despite the promising nature of current research, which predominantly focuses on animal models, the stimulation of neurogenesis in humans and its translation into effective treatment strategies encounter substantial challenges. Notably, the integration of multi-omics data, epigenetic regulation, and the interactions of the gut-brain axis could lead to the development of novel treatment approaches that either promote neuroregeneration or slow disease progression. However, the translation of these findings into clinical practice is impeded by numerous obstacles, including ethical concerns and the necessity for improved human tissue models. In the future, the integration of genetic, epigenetic, and microbiome data will be crucial for the development of safe and effective treatments.

Finally, the role of multi-omics in adult neurogenesis research still leaves much room for exploration. Adult neurogenesis may be a multifactorial condition in which gene-gene and gene-environment interactions play an important role. Therefore, understanding of these complex biological processes is more likely to be achieved using multidimensional multi-omics approaches.

CRediT authorship contribution statement

Jin Li: Writing – original draft, Data curation. **Leyi Huang:** Writing – original draft, Data curation. **Wenjie Xiao:** Visualization. **Jingyi Kong:** Visualization. **Minghua Hu:** Writing – review & editing, Conceptualization. **Aihua Pan:** Writing – review & editing. **Xiaoxin Yan:** Writing – review & editing. **Fulian Huang:** Validation, Methodology. **Lily Wan:** Writing – review & editing, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Data availability

All data generated or analyzed during this study are included in this published article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Funding: This study was supported by the Natural Science Foundation of Hunan Province (#2025JJ50479) and Undergraduate Innovation and Enterprise Training Project of China (X202410533611 and S202410533120).

References

[1] H.G. Kuhn, T. Toda, F.H. Gage, Adult hippocampal neurogenesis: a coming-of-age story, J. Neurosci. 38 (49) (2018) 10401–10410.
[2] A.M. Colangelo, G. Cirillo, L. Alberghina, M. Papa, H.V. Westerhoff, Neural plasticity and adult neurogenesis: the deep biology perspective, Neural Regen Res 14 (2) (2019) 201–205.
[3] J. Altman, G.D. Das, Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats, J. Comp. Neurol. 124 (3) (1965) 319–335.

[4] M. Carli, S. Aringhieri, S. Kolachalam, B. Longoni, G. Grenno, M. Rossi, A. Gemignani, F. Fornai, R. Maggio, M. Scarselli, Is adult hippocampal neurogenesis really relevant for the treatment of psychiatric disorders? Curr. Neuropharmacol. 19 (10) (2021) 1640–1660.
[5] J. Altman, G.D. Das, Post-natal origin of microneurones in the rat brain, Nature 207 (5000) (1965) 953–956.
[6] M.A. Costa, The endocrine function of human placenta: an overview, Reprod. Biomed. Online 32 (1) (2016) 14–43.
[7] Grattan Dr, The actions of prolactin in the brain during pregnancy and lactation, Prog. Brain Res. 133 (2001) 153–171.
[8] L. Torner, I.D. Neumann, The brain prolactin system: involvement in stress response adaptations in lactation, Stress 5 (4) (2002) 249–257.
[9] Y. Zhou, Y. Su, S. Li, B.C. Kennedy, D.Y. Zhang, A.M. Bond, Y. Sun, F. Jacob, L. Lu, P. Hu, A.N. Viaene, I. Helbig, S.K. Kessler, T. Lucas, R.D. Salinas, X. Gu, H. I. Chen, H. Wu, J.E. Kleinman, T.M. Hyde, D.W. Nauen, D.R. Weinberger, G.L. Ming, H. Song, Molecular landscapes of human hippocampal immature neurons across lifespan, Nature 607 (7919) (2022) 527–533.
[10] Z. Xiang, J. Li, D. Lu, X. Wei, X. Xu, Advances in multi-omics research on viral hepatitis, Front. Microbiol. 13 (2022) 987324.
[11] J. Liu, C. Xia, G. Wang, Multi-omics analysis in initiation and progression of meningiomas: from pathogenesis to diagnosis, Front. Oncol. 10 (2020) 1491.
[12] I. Subramanian, S. Verma, S. Kumar, A. Jere, K. Anamika, Multi-omics data integration, interpretation, and its application, Bioinform Biol Insights 14 (2020) 1177932219899051.
[13] L. Niu, K. Sulek, C.G. Vasilopoulou, A. Santos, NJ Wewer Albrechtsen, S. Rasmussen, F. Meier, M. Mann, Defining NASH from a multi-omics systems biology perspective, J. Clin. Med. 10 (20) (2021).
[14] J. Yan, S.L. Risacher, L. Shen, A.J. Saykin, Network approaches to systems biology analysis of complex disease: integrative methods for multi-omics data, Brief Bioinform 19 (6) (2018) 1370–1381.
[15] Y. Hasin, M. Seldin, A. Lusis, Multi-omics approaches to disease, Genome Biol. 18 (1) (2017) 83.
[16] R. Bocchi, G. Masserdotti, M. Gotz, Direct neuronal reprogramming: fast forward from new concepts toward therapeutic approaches, Neuron 110 (3) (2022) 366–393.
[17] B. Mossink, M. Negwer, D. Schubert, N Nadif Kasri, The emerging role of chromatin remodelers in neurodevelopmental disorders: a developmental perspective, Cell. Mol. Life Sci. 78 (6) (2021) 2517–2563.
[18] W. Liu, X. Liao, Z. Luo, Y. Yang, M.C. Lau, Y. Jiao, X. Shi, W. Zhai, H. Ji, J. Yeong, J. Liu, Probabilistic embedding, clustering, and alignment for integrating spatial transcriptomics data with PRECAST, Nat. Commun. 14 (1) (2023) 296.
[19] B. Velten, J.M. Braunger, R. Argelaguet, D. Arnol, J. Wirbel, D. Bredikhin, G. Zeller, O. Stegle, Identifying temporal and spatial patterns of variation from multimodal data using MEFISTO, Nat. Methods 19 (2) (2022) 179–186.
[20] M. Quesnel-Vallieres, M. Irimia, S.P. Cordes, B.J. Blencowe, Essential roles for the splicing regulator nSR100/SRRM4 during nervous system development, Genes Dev. 29 (7) (2015) 746–759.
[21] X. Chen, A.S. Tsvetkov, H.M. Shen, C. Isidoro, N.T. Ktistakis, A. Linkermann, W.J.H. Koopman, H.U. Simon, L. Galluzzi, S. Luo, D. Xu, W. Gu, O. Peulen, Q. Cai, D.C. Rubinsztein, J.T. Chi, D.D. Zhang, C. Li, S. Toyokuni, J. Liu, J.L. Roh, E. Dai, G. Juhasz, W. Liu, J. Zhang, M. Yang, J. Liu, L.Q. Zhu, W. Zou, M. Piacentini, W.X. Ding, Z. Yue, Y. Xie, M. Petersen, D.A. Gewirtz, M.A. Mandell, C.T. Chu, D. Sinha, E. Eftekharpour, B. Zhivotovsky, S. Besteiro, D.I. Gabrilovich, D.H. Kim, V.E. Kagan, H. Bayir, G.C. Chen, S. Ayton, J.D. Lünemann, M. Komatsu, S. Krautwald, B. Loos, E.H. Baehrecke, J. Wang, J.D. Lane, J. Sadoshima, W.S. Yang, M. Gao, C. Münz, M. Thumm, M. Kampmann, D. Yu, M.M. Lipinski, J.W. Jones, X. Jiang, H.J. Zeh, R. Kang, D.J. Klionsky, G. Kroemer, D. Tang, International consensus guidelines for the definition, detection, and interpretation of autophagy-dependent ferroptosis, Autophagy 20 (6) (2024) 1213–1246.
[22] D.B. Mahat, N.D. Tippens, J.D. Martin-Rufino, S.K. Waterton, J. Fu, S.E. Blatt, P.A. Sharp, Single-cell nascent RNA sequencing unveils coordinated global transcription, Nature 631 (8019) (2024) 216–223.
[23] B. Kara, Ö. Ayhan, G. Gökçay, N. Başboğaoğlu, A. Tolun, Adult phenotype and further phenotypic variability in SRD5A3-CDG, BMC Med. Genet. 15 (10) (2014).
[24] B. Chan, M. Clasquin, G.A. Smolen, G. Histen, J. Powe, Y. Chen, Z. Lin, C. Lu, Y. Liu, Y. Cang, Z. Yan, Y. Xia, R. Thompson, C. Singleton, M. Dorsch, L. Silverman, S.M. Su, H.H. Freeze, S. Jin, A mouse model of a human congenital disorder of glycosylation caused by loss of PMM2, Hum. Mol. Genet. 25 (11) (2016) 2182–2193.
[25] P.Q. Duy, S.C. Weise, C. Marini, X.J. Li, D. Liang, P.J. Dahl, S. Ma, A. Spajic, W. Dong, J. Juusola, E. Kiziltug, A.J. Kundishora, S. Koundal, M.Z. Pedram, L. A. Torres-Fernandez, K. Handler, E. De Domenico, M. Becker, T. Ulas, S.A. Juranek, E. Cuevas, L.T. Hao, B. Jux, A.M.M. Sousa, F. Liu, S.K. Kim, M. Li, Y. Yang, Y. Takeo, A. Duque, C. Nelson-Williams, Y. Ha, K. Selvaganesan, S.M. Robert, A.K. Singh, G. Allington, C.G. Furey, A.T. Timberlake, B.C. Reeves, H. Smith, A. Dunbar, T. DeSpenza Jr., J. Goto, A. Marlier, A. Moreno-De-Luca, X. Yu, W.E. Butler, B.S. Carter, E.M.R. Lake, R.T. Constable, P. Rakic, H. Lin, E. Deniz, H. Benveniste, N.S. Malvankar, J.I. Estrada-Veras, C.A. Walsh, S.L. Alper, J.L. Schultze, K. Paeschke, A. Doetzlhofer, F.G. Wulczyn, S.C. Jin, R.P. Lifton, N. Sestan, W. Kolanus, K.T. Kahle, Impaired neurogenesis alters brain biomechanics in a neuroprogenitor-based genetic subtype of congenital hydrocephalus, Nat. Neurosci. 25 (4) (2022) 458–473.
[26] M.L. Tornesello, R. Faraonio, L. Buonaguro, C. Annunziata, N. Starita, A. Cerasuolo, F. Pezzuto, A.L. Tornesello, F.M. Buonaguro, The role of microRNAs, long non-coding RNAs, and circular RNAs in cervical cancer, Front. Oncol. 10 (2020) 150.
[27] M.A. Quezada-Ramirez, R. Castaneda-Arellano, G. Perez-Sanchez, J. Hernandez-Soto, J. Segovia, The Growth arrest specific 1 (Gas1) gene is transcriptionally regulated by NeuroD1 via two distal E-boxes, Exp. Cell Res. 363 (2) (2018) 332–341.
[28] D. Nesan, D.M. Kurrasch, Gestational exposure to common endocrine disrupting chemicals and their impact on neurodevelopment and behavior, Annu. Rev. Physiol. 82 (2020) 177–202.
[29] A.D. Henriksen, A. Andrade, E.P. Harris, E.F. Rissman, J.T. Wolstenholme, Bisphenol a exposure in utero disrupts hypothalamic gene expression particularly genes suspected in autism spectrum disorders and neuron and hormone signaling, Int. J. Mol. Sci. 21 (9) (2020).
[30] G.M. Mancini, R. Schot, M.C. de Wit, R.F. de Coo, R. Oostenbrink, K. Bindels-de Heus, L.P. Berger, M.H. Lequin, F.A. de Vries, M. Wilke, MA van Slegtenhorst, CSTB null mutation associated with microcephaly, early developmental delay, and severe dyskinesia, Neurology 86 (9) (2016) 877–878.
[31] J.L. Gallop, Filopodia and their links with membrane traffic and cell adhesion, Semin. Cell Dev. Biol. 102 (2020) 81–89.
[32] E.G. Overbey, et al., The space omics and medical atlas (SOMA) and international astronaut biobank, Nature 632 (8027) (2024) 1145–1154.
[33] N. Murao, T. Matsuda, H. Kadowaki, Y. Matsushita, K. Tanimoto, T. Katagiri, K. Nakashima, H. Nishitoh, The Derlin-1-Stat5b axis maintains homeostasis of adult hippocampal neurogenesis, EMBO Rep 25 (8) (2024) 3678–3706.
[34] M. Fukuda, Y. Fujita, Y. Hino, M. Nakao, K. Shirahige, T. Yamashita, Inhibition of HDAC8 reduces the proliferation of adult neural stem cells in the subventricular zone, Int. J. Mol. Sci. 25 (5) (2024).
[35] Y. Wang, L. Lin, H. Lai, L.F. Parada, L. Lei, Transcription factor Sox11 is essential for both embryonic and adult neurogenesis, Dev. Dyn. 242 (6) (2013) 638–653.
[36] N. Spassky, F.T. Merkle, N. Flames, A.D. Tramontin, J.M. Garcia-Verdugo, A. Alvarez-Buylla, Adult ependymal cells are postmitotic and are derived from radial glial cells during embryogenesis, J. Neurosci. 25 (1) (2005) 10–18.
[37] B. Tuysuz, D. Pehlivan, A. Ozkok, S. Jhangiani, C. Yalcinkaya, C.A. Zeybek, D.M. Muzny, J.R. Lupski, R. Gibbs, J. Jaeken, Phenotypic expansion of congenital disorder of glycosylation due to SRD5A3 null mutation, JIMD Rep 26 (2016) 7–12.
[38] M. Schiff, C. Roda, M.L. Monin, A. Arion, M. Barth, N. Bednarek, M. Bidet, C. Bloch, N. Boddaert, D. Borgel, A. Brassier, A. Brice, A. Bruneel, R. Buissonniere, B. Chabrol, M.C. Chevalier, V. Cormier-Daire, C. De Barace, E. De Maistre, A. De Saint-Martin, N. Dorison, V. Drouin-Garraud, T. Dupre, B. Echenne, P. Edery, F. Feillet, I. Fontan, C. Francannet, F. Labarthe, C. Gitiaux, D. Heron, M. Hully, S. Lamoureux, D. Martin-Coignard, C. Mignot, G. Morin, T. Pascreau, O. Pincemaille, M. Polak, A. Roubertie, C. Thauvin-Robinet, A. Toutain, G. Viot, S. Vuillaumier-Barrot, N. Seta, P. De Lonlay, Clinical, laboratory and molecular findings and long-term follow-up data in 96 French patients with PMM2-CDG (phosphomannomutase 2-congenital disorder of glycosylation) and review of the literature, J. Med. Genet. 54 (12) (2017) 843–851.
[39] P.A. Weisner, C.Y. Chen, Y. Sun, J. Yoo, W.C. Kao, H. Zhang, E.T. Baltz, J.M. Troy, L. Stubbs, A mouse mutation that dysregulates neighboring Galnt17 and Auts2 genes is associated with phenotypes related to the human AUTS2 syndrome, G3 (Bethesda) 9 (11) (2019) 3891–3906.

[40] F. Di Matteo, F. Pipicelli, C. Kyrousi, I. Tovecci, E. Penna, M. Crispino, A. Chambery, R. Russo, A.C. Ayo-Martin, M. Giordano, A. Hoffmann, E. Ciusani, L. Canafoglia, M. Gotz, R. Di Giaimo, S. Cappello, Cystatin B is essential for proliferation and interneuron migration in individuals with EPM1 epilepsy, EMBO Mol. Med. 12 (6) (2020) e11419.

[41] X. Zhu, Y. Joo, S. Bossi, R.A. McDevitt, A. Xie, Y. Wang, Y. Xue, S. Su, S.K. Lee, N. Sah, S. Zhang, R. Ye, A. Pinto, Y. Zhang, K. Araki, M. Araki, M. Morales, M. P. Mattson, H van Praag, W. Wang, Tdrd3-null mice show post-transcriptional and behavioral impairments associated with neurogenesis and synaptic plasticity, Prog Neurobiol 233 (2024) 102568.

[42] C. Sierra, M. Sabariego-Navarro, Á. Fernández-Blanco, S. Cruciani, A. Zamora-Moratalla, E.M. Novoa, M. Dierssen, The lncRNA Snhg11, a new candidate contributing to neurogenesis, plasticity, and memory deficits in Down syndrome, Mol Psychiatry 29 (7) (2024) 2117–2134.

[43] L. Whitton, D. Cosgrove, C. Clarkson, D. Harold, K. Kendall, A. Richards, K. Mantripragada, M.J. Owen, M.C.O. Donovan, J. Walters, A. Hartmann, B. Konte, D. Rujescu, Wtccc, M. Gill, A. Corvin, S. Rea, G. Donohoe, D.W. Morris, Cognitive analysis of schizophrenia risk genes that function as epigenetic regulators of gene expression, Am J Med Genet B Neuropsychiatr Genet 171 (8) (2016) 1170–1179.

[44] D. Weichenhan, D.B. Lipka, P. Lutsik, A. Goyal, C. Plass, Epigenomic technologies for precision oncology, Semin. Cancer Biol. 84 (2022) 60–68.

[45] X. Liu, B. Fan, M. Chopp, Z. Zhang, Epigenetic mechanisms underlying adult post stroke neurogenesis, Int. J. Mol. Sci. 21 (17) (2020).

[46] S. Kunoh, H. Nakashima, K. Nakashima, Epigenetic regulation of neural stem cells in developmental and adult stages, Epigenomes 8 (2) (2024).

[47] M. Baumgart, M. Groth, S. Priebe, A. Savino, G. Testa, A. Dix, R. Ripa, F. Spallotta, C. Gaetano, M. Ori, E Terzibasi Tozzini, R. Guthke, M. Platzer, A. Cellerino, RNA-seq of the aging brain in the short-lived fish N. furzeri - conserved pathways and novel genes associated with neurogenesis, Aging Cell 13 (6) (2014) 965–974.

[48] A. Ocampo, P. Reddy, P. Martinez-Redondo, A. Platero-Luengo, F. Hatanaka, T. Hishida, M. Li, D. Lam, M. Kurita, E. Beyret, T. Araoka, E. Vazquez-Ferrer, D. Donoso, J.L. Roman, J. Xu, C Rodriguez Esteban, G. Nunez, E Nunez Delicado, J.M. Campistol, I. Guillen, P. Guillen, JC Izpisua Belmonte, In vivo amelioration of age-associated hallmarks by partial reprogramming, CELL 167 (7) (2016) 1719–1733, e1712.

[49] A. Rodriguez-Matellan, N. Alcazar, F. Hernandez, M. Serrano, J. Avila, In vivo reprogramming ameliorates aging features in dentate gyrus cells and improves memory in mice, Stem Cell Rep. 15 (5) (2020) 1056–1066.

[50] S. Horvath, Y. Zhang, P. Langfelder, R.S. Kahn, M.P. Boks, K. van Eijk, LH van den Berg, R.A. Ophoff, Aging effects on DNA methylation modules in human brain and blood tissue, Genome Biol. 13 (10) (2012) R97.

[51] S. Zocher, R.W. Overall, M. Lesche, A. Dahl, G. Kempermann, Environmental enrichment preserves a young DNA methylation landscape in the aged mouse hippocampus, Nat. Commun. 12 (1) (2021) 3892.

[52] S. Zocher, R.W. Overall, G. Berdugo-Vega, N. Rund, A. Karasinsky, V.S. Adusumilli, C. Steinhauer, S. Scheibenstock, K. Handler, J.L. Schultze, F. Calegari, G. Kempermann, De novo DNA methylation controls neuronal maturation during adult hippocampal neurogenesis, EMBO J. 40 (18) (2021) e107100.

[53] D.K. Ma, M.H. Jang, J.U. Guo, Y. Kitabatake, M.L. Chang, N. Pow-Anpongkul, R.A. Flavell, B. Lu, G.L. Ming, H. Song, Neuronal activity-induced Gadd45b promotes epigenetic DNA demethylation and adult neurogenesis, SCIENCE. 323 (5917) (2009) 1074–1077.

[54] X. Cao, G. Yeo, A.R. Muotri, T. Kuwabara, F.H. Gage, Noncoding RNAs in the mammalian central nervous system, Annu. Rev. Neurosci. 29 (2006) 77–103.

[55] C. Zhao, G. Sun, S. Li, Y. Shi, A feedback regulatory loop involving microRNA-9 and nuclear receptor TLX in neural stem cell fate determination, Nat. Struct. Mol. Biol. 16 (4) (2009) 365–371.

[56] A. Welle, C.V. Kasakow, A.M. Jungmann, D. Gobbo, L. Stopper, K. Nordstrom, A. Salhab, G. Gasparoni, A. Scheller, F. Kirchhoff, J. Walter, Epigenetic control of region-specific transcriptional programs in mouse cerebellar and cortical astrocytes, Glia 69 (9) (2021) 2160–2177.

[57] HDi Consortium, Developmental alterations in Huntington's disease neural cells and pharmacological rescue in cells and mice, Nat. Neurosci. 20 (5) (2017) 648–660.

[58] S. Horie, E. Kiyokage, S. Hayashi, K. Inoue, J. Sohn, H. Hioki, T. Furuta, K. Toida, Structural basis for noradrenergic regulation of neural circuits in the mouse olfactory bulb, J. Comp. Neurol. 529 (9) (2021) 2189–2208.

[59] J. Lötsch, E. Schaeffeler, M. Mittelbronn, S. Winter, V. Gudziol, S.W. Schwarzacher, T. Hummel, A. Doehring, M. Schwab, A. Ultsch, Functional genomics suggest neurogenesis in the adult human olfactory bulb, Brain Struct. Funct. 219 (6) (2014) 1991–2000.

[60] T.J. Schoenfeld, H.C. McCausland, H.D. Morris, V. Padmanaban, H.A. Cameron, Stress and loss of adult neurogenesis differentially reduce hippocampal volume, Biol. Psychiatry 82 (12) (2017) 914–923.

[61] T.R. Powell, T. Murphy, S.H. Lee, R.R.R. Duarte, H.A. Lee, D. Smeeth, J. Price, G. Breen, S. Thuret, Inter-individual variation in genes governing human hippocampal progenitor differentiation in vitro is associated with hippocampal volume in adulthood, Sci. Rep. 7 (1) (2017) 15112.

[62] A.C. Apple, A. Oddi, M.J. Peluso, B.M. Asken, T.J. Henrich, J.D. Kelly, S.J. Pleasure, S.G. Deeks, I.E. Allen, J.N. Martin, L.C. Ndhlovu, B.L. Miller, M. L. Stephens, J. Hellmuth, Risk factors and abnormal cerebrospinal fluid associate with cognitive symptoms after mild COVID-19, Ann Clin Transl Neurol 9 (2) (2022) 221–226.

[63] H. Sari, R. Galbusera, G. Bonnier, Y. Lin, Z. Alshelh, A. Torrado-Carvajal, S.S. Mukerji, E.M. Ratai, R.T. Gandhi, J.T. Chu, O. Akeju, V. Orhurhu, A.N. Salvatore, J. Sherman, D.S. Kwon, B. Walker, B. Rosen, J.C. Price, L.E. Pollak, M.L. Loggia, C. Granziera, Multimodal investigation of neuroinflammation in aviremic patients with HIV on antiretroviral therapy and HIV elite controllers, Neurol Neuroimmunol Neuroinflamm 9 (2) (2022).

[64] T. Meng, X. Chen, Z. He, H. Huang, S. Lin, K. Liu, G. Bai, H. Liu, M. Xu, H. Zhuang, Y. Zhang, A. Waqas, Q. Liu, C. Zhang, X.D. Sun, H. Huang, M. Umair, Y. Yan, D. Feng, ATP9A deficiency causes ADHD and aberrant endosomal recycling via modulating RAB5 and RAB11 activity, Mol Psychiatry 28 (3) (2023) 1219–1231.

[65] E. D'Haene, E.Z. Jacobs, P.J. Volders, T. De Meyer, B. Menten, S. Vergult, Identification of long non-coding RNAs involved in neuronal development and intellectual disability, Sci. Rep. 6 (2016) 28396.

[66] M. Dai, S. Radhakrishnan, R. Li, R. Tan, K. Yan, G. Fan, M. Liu, Targeted protein degradation: an important tool for drug discovery for "undruggable" tumor transcription factors, Technol. Cancer Res. Treat. 21 (2022) 15330338221095950.

[67] N. Usui, S. Berto, A. Konishi, M. Kondo, G. Konopka, H. Matsuzaki, S. Shimada, Zbtb16 regulates social cognitive behaviors and neocortical development, Transl. Psychiatry 11 (1) (2021) 242.

[68] C. Schneider, R.M. King, L. Philipson, Genes specifically expressed at growth arrest of mammalian cells, CELL 54 (6) (1988) 787–793.

[69] A. Fleming, M. Bourdenx, M. Fujimaki, C. Karabiyik, G.J. Krause, A. Lopez, A. Martin-Segura, C. Puri, A. Scrivo, J. Skidmore, S.M. Son, E. Stamatakou, L. Wrobel, Y. Zhu, A.M. Cuervo, D.C. Rubinsztein, The different autophagy degradation pathways and neurodegeneration, Neuron 110 (6) (2022) 935–966.

[70] R. Geffin, R. Martinez, A. de Las Pozas, B. Issac, M. McCarthy, Apolipoprotein E4 suppresses neuronal-specific gene expression in maturing neuronal progenitor cells exposed to HIV, J. Neuroimmune Pharmacol. 12 (3) (2017) 462–483.

[71] A. Stozer, E. Paradiz Leitgeb, V. Pohorec, J. Dolensek, L Krizancic Bombek, M. Gosak, M Skelin Klemen, The role of cAMP in beta cell stimulus-secretion and intercellular coupling, Cells 10 (7) (2021).

[72] H. Chen, Y. He, S. Chen, S. Qi, J. Shen, Therapeutic targets of oxidative/nitrosative stress and neuroinflammation in ischemic stroke: applications for natural product efficacy with omics and systemic biology, Pharmacol. Res. 158 (2020) 104877.

[73] G. La Manno, R. Soldatov, A. Zeisel, E. Braun, H. Hochgerner, V. Petukhov, K. Lidschreiber, M.E. Kastriti, P. Lönnerberg, A. Furlan, J. Fan, L.E. Borm, Z. Liu, D. van Bruggen, J. Guo, X. He, R. Barker, E. Sundström, G. Castelo-Branco, P. Cramer, I. Adameyko, S. Linnarsson, P.V. Kharchenko, RNA velocity of single cells, Nature 560 (7719) (2018) 494–498.

[74] G. Marcy, L. Foucault, E. Babina, T. Capeliez, E. Texeraud, S. Zweifel, C. Heinrich, H. Hernandez-Vargas, C. Parras, D. Jabaudon, O. Raineteau, Single-cell analysis of the postnatal dorsal V-SVZ reveals a role for Bmpr1a signaling in silencing pallial germinal activity, Sci. Adv. 9 (18) (2023) eabq7553.

[75] D.J. Di Bella, E. Habibi, R.R. Stickels, G. Scalia, J. Brown, P. Yadollahpour, S.M. Yang, C. Abbate, T. Biancalani, E.Z. Macosko, F. Chen, A. Regev, P. Arlotta, Molecular logic of cellular diversification in the mouse cerebral cortex, Nature 595 (7868) (2021) 554–559.

[76] R.S. Ziffra, C.N. Kim, J.M. Ross, A. Wilfert, T.N. Turner, M. Haeussler, A.M. Casella, P.F. Przytycki, K.C. Keough, D. Shin, D. Bogdanoff, A. Kreimer, K. S. Pollard, S.A. Ament, E.E. Eichler, N. Ahituv, T.J. Nowakowski, Single-cell epigenomics reveals mechanisms of human cortical development, Nature 598 (7879) (2021) 205–213.

[77] C.A. Herring, R.K. Simmons, S. Freytag, D. Poppe, J.J.D. Moffet, J. Pflueger, S. Buckberry, D.B. Vargas-Landin, O. Clément, E.G. Echeverría, G.J. Sutton, A. Alvarez-Franco, R. Hou, C. Pflueger, K. McDonald, J.M. Polo, A.R.R. Forrest, A.K. Nowak, I. Voineagu, L. Martelotto, R. Lister, Human prefrontal cortex gene regulatory dynamics from gestation to adulthood at single-cell resolution, Cell 185 (23) (2022) 4428–4447.e4428.
[78] E. Magrinelli, N. Baumann, R.J. Wagener, C. Glangetas, C. Bellone, D. Jabaudon, E. Klingler, Heterogeneous fates of simultaneously-born neurons in the cortical ventricular zone, Sci. Rep. 12 (1) (2022) 6022.
[79] U.C. Eze, A. Bhaduri, M. Haeussler, T.J. Nowakowski, A.R. Kriegstein, Single-cell atlas of early human brain development highlights heterogeneity of human neuroepithelial cells and early radial glia, Nat. Neurosci. 24 (4) (2021) 584–594.
[80] K.A. Aldinger, Z. Thomson, I.G. Phelps, P. Haldipur, M. Deng, A.E. Timms, M. Hirano, G. Santpere, C. Roco, A.B. Rosenberg, B. Lorente-Galdos, F.O. Gulden, D. O'Day, L.M. Overman, S.N. Lisgo, P. Alexandre, N. Sestan, D. Doherty, W.B. Dobyns, G. Seelig, I.A. Glass, K.J. Millen, Spatial and cell type transcriptional landscape of human cerebellar development, Nat. Neurosci. 24 (8) (2021) 1163–1175.
[81] H. Peng, P. Xie, L. Liu, X. Kuang, Y. Wang, L. Qu, H. Gong, S. Jiang, A. Li, Z. Ruan, L. Ding, Z. Yao, C. Chen, M. Chen, T.L. Daigle, R. Dalley, Z. Ding, Y. Duan, A. Feiner, P. He, C. Hill, K.E. Hirokawa, G. Hong, L. Huang, S. Kebede, H.C. Kuo, R. Larsen, P. Lesnar, L. Li, Q. Li, X. Li, Y. Li, Y. Li, A. Liu, D. Lu, S. Mok, L. Ng, T.N. Nguyen, Q. Ouyang, J. Pan, E. Shen, Y. Song, S.M. Sunkin, B. Tasic, M.B. Veldman, W. Wakeman, W. Wan, P. Wang, Q. Wang, T. Wang, Y. Wang, F. Xiong, W. Xiong, W. Xu, M. Ye, L. Yin, Y. Yu, J. Yuan, J. Yuan, Z. Yun, S. Zeng, S. Zhang, S. Zhao, Z. Zhao, Z. Zhou, Z.J. Huang, L. Esposito, M.J. Hawrylycz, S. A. Sorensen, X.W. Yang, Y. Zheng, Z. Gu, W. Xie, C. Koch, Q. Luo, J.A. Harris, Y. Wang, H. Zeng, Morphological diversity of single neurons in molecularly defined cell types, Nature 598 (7879) (2021) 174–181.
[82] D.W. Kim, E. Place, K. Chinnaiya, E. Manning, C. Sun, W. Dai, I. Groves, K. Ohyama, S. Burbridge, M. Placzek, S. Blackshaw, Single-cell analysis of early chick hypothalamic development reveals that hypothalamic cells are induced from prethalamic-like progenitors, Cell Rep. 38 (3) (2022) 110251.
[83] K. Lust, A. Maynard, T. Gomes, J.S. Fleck, J.G. Camp, E.M. Tanaka, B. Treutlein, Single-cell analyses of axolotl telencephalon organization, neurogenesis, and regeneration, Science. 377 (6610) (2022) eabp9262.
[84] S.R. Srivatsan, M.C. Regier, E. Barkan, J.M. Franks, J.S. Packer, P. Grosjean, M. Duran, S. Saxton, J.J. Ladd, M. Spielmann, C. Lois, P.D. Lampe, J. Shendure, K. R. Stevens, C. Trapnell, Embryo-scale, single-cell spatial transcriptomics, Science 373 (6550) (2021) 111–117.
[85] P. Bielefeld, A. Martirosyan, S. Martín-Suárez, A. Apresyan, G.F. Meerhoff, F. Pestana, S. Poovathingal, N. Reijner, W. Koning, R.A. Clement, I. Van der Veen, E. M. Toledo, O. Polzer, I. Durá, S. Hovhannisyan, B.S. Nilges, A. Bogdoll, N.D. Kashikar, P.J. Lucassen, T.G. Belgard, J.M. Encinas, M.G. Holt, C.P. Fitzsimons, Traumatic brain injury promotes neurogenesis at the cost of astrogliogenesis in the adult hippocampus of male mice, Nat. Commun. 15 (1) (2024) 5222.
[86] Y. Shi, M. Wang, D. Mi, T. Lu, B. Wang, H. Dong, S. Zhong, Y. Chen, L. Sun, X. Zhou, Q. Ma, Z. Liu, W. Wang, J. Zhang, Q. Wu, O. Marín, X. Wang, Mouse and human share conserved transcriptional programs for interneuron development, Science. 374 (6573) (2021) eabj6641.
[87] V.D. Bocchi, P. Conforti, E. Vezzoli, D. Besusso, C. Cappadona, T. Lischetti, M. Galimberti, V. Ranzani, R.J.P. Bonnal, M. De Simone, G. Rossetti, X. He, K. Kamimoto, I. Espuny-Camacho, A. Faedo, F. Gervasoni, R. Vuono, S.A. Morris, J. Chen, D. Felsenfeld, G. Pavesi, R.A. Barker, M. Pagani, E. Cattaneo, The coding and long noncoding single-cell atlas of the developing human fetal striatum, Science. 372 (6542) (2021).
[88] S. Bajaj, J.A. Bagley, C. Sommer, A. Vertesy, S Nagumo Wong, V. Krenn, J. Lévi-Strauss, J.A. Knoblich, Neurotransmitter signaling regulates distinct phases of multimodal human interneuron migration, Embo j. 40 (23) (2021) e108714.
[89] Y. Fu, M. Yang, H. Yu, Y. Wang, X. Wu, J. Yong, Y. Mao, Y. Cui, X. Fan, L. Wen, J. Qiao, F. Tang, Heterogeneity of glial progenitor cells during the neurogenesis-to-gliogenesis switch in the developing human cerebral cortex, Cell Rep. 34 (9) (2021) 108788.
[90] A. Fiorenzano, E. Sozzi, M. Birtele, J. Kajtez, J. Giacomoni, F. Nilsson, A. Bruzelius, Y. Sharma, Y. Zhang, B. Mattsson, J. Emnéus, D.R. Ottosson, P. Storm, M. Parmar, Single-cell transcriptomics captures features of human midbrain development and dopamine neuron diversity in brain organoids, Nat. Commun. 12 (1) (2021) 7302.
[91] W. Wang, H. Cho, J.W. Lee, S.K. Lee, The histone demethylase Kdm6b regulates subtype diversification of mouse spinal motor neurons during development, Nat. Commun. 13 (1) (2022) 958.
[92] K.C. Allaway, M.I. Gabitto, O. Wapinski, G. Saldi, C.Y. Wang, R.C. Bandler, S.J. Wu, R. Bonneau, G. Fishell, Genetic and epigenetic coordination of cortical interneuron development, Nature 597 (7878) (2021) 693–697.
[93] A. Bhaduri, C. Sandoval-Espinosa, M. Otero-Garcia, I. Oh, R. Yin, U.C. Eze, T.J. Nowakowski, A.R. Kriegstein, An atlas of cortical arealization identifies dynamic molecular signatures, Nature 598 (7879) (2021) 200–204.
[94] L. Senzel, D.V. Gnatenko, W.F. Bahou, The platelet proteome, Curr. Opin. Hematol. 16 (5) (2009) 329–333.
[95] E. Goncalves, R.C. Poulos, Z. Cai, S. Barthorpe, S.S. Manda, N. Lucas, A. Beck, D. Bucio-Noble, M. Dausmann, C. Hall, M. Hecker, J. Koh, H. Lightfoot, S. Mahboob, I. Mali, J. Morris, L. Richardson, A.J. Seneviratne, R. Shepherd, E. Sykes, F. Thomas, S. Valentini, S.G. Williams, Y. Wu, D. Xavier, K.L. MacKenzie, P.G. Hains, B. Tully, P.J. Robinson, Q. Zhong, Garnett Mj, Reddel Rr, Pan-cancer proteomic map of 949 human cell lines, Cancer Cell 40 (8) (2022) 835–849, e838.
[96] D. Kim, Y.S. Jo, H.S. Jo, S. Bae, Y.W. Kwon, Y.S. Oh, J.H. Yoon, Comparative phosphoproteomics of neuro-2a cells under insulin resistance reveals new molecular signatures of alzheimer's disease, Int. J. Mol. Sci. 23 (2) (2022).
[97] K. Jin, X.O. Mao, B. Cottrell, B. Schilling, L. Xie, R.H. Row, Y. Sun, A. Peel, J. Childs, G. Gendeh, B.W. Gibson, D.A. Greenberg, Proteomic and immunochemical characterization of a role for stathmin in adult neurogenesis, FASEB J. 18 (2) (2004) 287–299.
[98] S. Lugert, T. Kremer, R. Jagasia, A. Herrmann, S. Aigner, C. Giachino, I. Mendez-David, A.M. Gardier, J.P. Carralot, H. Meistermann, A. Augustin, M.D. Saxe, J. Lamerz, G. Duran-Pacheco, A. Ducret, V. Taylor, D.J. David, C. Czech, Glypican-2 levels in cerebrospinal fluid predict the status of adult hippocampal neurogenesis, Sci. Rep. 7 (2017) 46543.
[99] J. Kjell, J. Fischer-Sternjak, A.J. Thompson, C. Friess, M.J. Sticco, F. Salinas, J. Cox, D.C. Martinelli, J. Ninkovic, K. Franze, H.B. Schiller, M. Gotz, Defining the adult neural stem cell niche proteome identifies key regulators of adult neurogenesis, Cell Stem Cell 26 (2) (2020) 277–293, e278.
[100] P. Forcella, N. Ifflander, C. Rolando, E.A. Balta, A. Lampada, C. Giachino, T. Mukhtar, T. Bock, V. Taylor, SAFB regulates hippocampal stem cell fate by targeting Drosha to destabilize Nfib mRNA, Elife 13 (2024).
[101] A. Casciati, K. Dobos, F. Antonelli, A. Benedek, S.J. Kempf, M. Belles, A. Balogh, M. Tanori, L. Heredia, M.J. Atkinson, C. von Toerne, O. Azimzadeh, A. Saran, G. Safrany, M.A. Benotmane, M.V. Linares-Vidal, S. Tapio, K. Lumniczky, S. Pazzaglia, Age-related effects of X-ray irradiation on mouse hippocampus, Oncotarget 7 (19) (2016) 28040–28058.
[102] H. Park, J. Yang, R. Kim, Y. Li, Y. Lee, C. Lee, J. Park, D. Lee, H. Kim, E. Kim, Mice lacking the PSD-95-interacting E3 ligase, Dorfin/Rnf19a, display reduced adult neurogenesis, enhanced long-term potentiation, and impaired contextual fear conditioning, Sci. Rep. 5 (2015) 16410.
[103] P. Mol, O. Chatterjee, L. Gopalakrishnan, K.K. Mangalaparthi, F. Bhat, M. Kumar, B. Nair, S.K. Shankar, A. Mahadevan, T.S.K. Prasad, Age-associated molecular changes in human Hippocampus subfields as determined by quantitative proteomics, OMICS 26 (7) (2022) 382–391.
[104] O. Chatterjee, L. Gopalakrishnan, P. Mol, J. Advani, B. Nair, S.K. Shankar, A. Mahadevan, T.S.K. Prasad, The normal human adult hypothalamus proteomic landscape: rise of neuroproteomics in biological psychiatry and systems biology, OMICS 25 (11) (2021) 693–710.
[105] Y. Xu, N. Tamamaki, T. Noda, K. Kimura, Y. Itokazu, N. Matsumoto, M. Dezawa, C. Ide, Neurogenesis in the ependymal layer of the adult rat 3rd ventricle, Exp. Neurol. 192 (2) (2005) 251–264.
[106] M. Bolborea, N. Dale, Hypothalamic tanycytes: potential roles in the control of feeding and energy balance, Trends Neurosci. 36 (2) (2013) 91–100.
[107] E. Rojczyk-Golebiewska, A. Palasz, R. Wiaderkiewicz, Hypothalamic subependymal niche: a novel site of the adult neurogenesis, Cell. Mol. Neurobiol. 34 (5) (2014) 631–642.
[108] R.M. Fame, M.K. Lehtinen, Emergence and developmental roles of the cerebrospinal fluid system, Dev. Cell 52 (3) (2020) 261–275.
[109] A. Gato, M.I. Alonso, F. Lamus, J. Miyan, Neurogenesis: a process ontogenically linked to brain cavities and their content, CSF, Semin. Cell Dev. Biol. 102 (2020) 21–27.
[110] M.W. Zappaterra, M.K. Lehtinen, The cerebrospinal fluid: regulator of neurogenesis, behavior, and beyond, Cell. Mol. Life Sci. 69 (17) (2012) 2863–2878.
[111] E. Voukali, M. Vinkler, Proteomic-based evidence for adult neurogenesis in birds and mammals as indicated from cerebrospinal fluid, Neural Regen Res 17 (12) (2022) 2576–2581.

[112] E. Voukali, N.K. Veetil, P. Nemec, P. Stopka, M. Vinkler, Comparison of plasma and cerebrospinal fluid proteomes identifies gene products guiding adult neurogenesis and neural differentiation in birds, Sci. Rep. 11 (1) (2021) 5312.
[113] M. Schouten, S.A. Fratantoni, C.J. Hubens, S.R. Piersma, T.V. Pham, P. Bielefeld, R.A. Voskuyl, P.J. Lucassen, C.R. Jimenez, C.P. Fitzsimons, MicroRNA-124 and -137 cooperativity controls caspase-3 activity through BCL2L13 in hippocampal neural stem cells, Sci. Rep. 5 (2015) 12448.
[114] J.Y.W. Liu, N. Dzurova, B. Al-Kaaby, K. Mills, S.M. Sisodiya, M. Thom, Granule cell dispersion in human temporal lobe epilepsy: proteomics investigation of neurodevelopmental migratory pathways, Front. Cell. Neurosci. 14 (53) (2020).
[115] K. Khoramipour, O. Sandbakk, A.H. Keshteli, A.A. Gaeini, D.S. Wishart, K. Chamari, Metabolomics in exercise and sports: a systematic review, Sports Med. 52 (3) (2022) 547–583.
[116] C.H. Johnson, J. Ivanisevic, G. Siuzdak, Metabolomics: beyond biomarkers and towards mechanisms, Nat. Rev. Mol. Cell Biol. 17 (7) (2016) 451–459.
[117] A. D'Alessandro, C. Marrocco, S. Rinalducci, A. Peschiaroli, A.M. Timperio, L. Bongiorno-Borbone, A. Finazzi Agrò, G. Melino, L. Zolla, Analysis of TAp73-dependent signaling via omics technologies, J. Proteome Res. 12 (9) (2013) 4207–4220.
[118] S. Balentova, P. Hnilicova, D. Kalenska, E. Baranovicova, P. Murin, M. Bittsansky, E. Hajtmanova, J. Lehotsky, M. Adamkov, Metabolic and histopathological changes in the brain and plasma of rats exposed to fractionated whole-brain irradiation, Brain Res. 1708 (2019) 146–159.
[119] A.L. Hillje, E. Beckmann, M.A. Pavlou, C. Jaeger, M.P. Pacheco, T. Sauter, J.C. Schwamborn, L. Lewejohann, The neural stem cell fate determinant TRIM32 regulates complex behavioral traits, Front. Cell. Neurosci. 9 (75) (2015).
[120] C.C. Bortolasci, B. Spolding, S. Kidnapillai, T. Connor, T.T.T. Truong, Z.S.J. Liu, B. Panizzutti, M.F. Richardson, L. Gray, M. Berk, O.M. Dean, K. Walder, Transcriptional effects of psychoactive drugs on genes involved in neurogenesis, Int. J. Mol. Sci. 21 (21) (2020).
[121] S. Nicolas, S. Dohm-Hansen, A. Lavelle, T.F.S. Bastiaanssen, J.A. English, J.F. Cryan, Y.M. Nolan, Exercise mitigates a gut microbiota-mediated reduction in adult hippocampal neurogenesis and associated behaviours in rats, Transl. Psychiatry 14 (1) (2024) 195.
[122] P. Sun, M. Wang, Z. Li, J. Wei, F. Liu, W. Zheng, X. Zhu, X. Chai, S. Zhao, Eucommiae cortex polysaccharides mitigate obesogenic diet-induced cognitive and social dysfunction via modulation of gut microbiota and tryptophan metabolism, Theranostics 12 (8) (2022) 3637–3655.
[123] Y.H. Yan, Z.H. Huang, Q.P. Xiong, Y.W. Song, S.Y. Li, B.W. Yang, L. Sun, M.Y. Zhang, Y. Ji, Effects of Broussonetia papyrifera (L.) L'Her. ex Vent. fruits water extract on hippocampal neurogenesis in the treatment of APP/PS1 transgenic mice, Front. Pharmacol. 13 (2022) 1056614.
[124] P. Rana, M. Gupta, A.R. Khan, B.S. Hemanth Kumar, R. Roy, S. Khushu, NMR based metabolomics reveals acute hippocampal metabolic fluctuations during cranial irradiation in murine model, Neurochem. Int. 74 (1–7) (2014).
[125] M. Audano, S. Pedretti, M. Crestani, D. Caruso, E. De Fabiani, N. Mitro, Mitochondrial dysfunction increases fatty acid beta-oxidation and translates into impaired neuroblast maturation, FEBS Lett. 593 (22) (2019) 3173–3189.
[126] R. Vitali, C. Prioreschi, L. Lorenzo Rebenaque, E. Colantoni, D. Giovannini, S. Frusciante, G. Diretto, F. Marco-Jimenez, M. Mancuso, A. Casciati, S. Pazzaglia, Gut-brain Axis: insights from hippocampal neurogenesis and brain tumor development in a mouse model of experimental colitis induced by dextran sodium sulfate, Int. J. Mol. Sci. 23 (19) (2022).
[127] G. Sharon, T.R. Sampson, D.H. Geschwind, S.K. Mazmanian, The central nervous system and the gut microbiome, Cell 167 (4) (2016) 915–932.
[128] S. Grabrucker, M. Marizzoni, E. Silajdžić, N. Lopizzo, E. Mombelli, S. Nicolas, S. Dohm-Hansen, C. Scassellati, D.V. Moretti, M. Rosa, K. Hoffmann, J.F. Cryan, O.F. O'Leary, J.A. English, A. Lavelle, C. O'Neill, S. Thuret, A. Cattaneo, Y.M. Nolan, Microbiota from Alzheimer's patients induce deficits in cognition and hippocampal neurogenesis, Brain 146 (12) (2023) 4916–4934.
[129] J.F. Cryan, K.J. O'Riordan, C.S.M. Cowan, K.V. Sandhu, T.F.S. Bastiaanssen, M. Boehme, M.G. Codagnone, S. Cussotto, C. Fulling, A.V. Golubeva, K. E. Guzzetta, M. Jaggar, C.M. Long-Smith, J.M. Lyte, J.A. Martin, A. Molinero-Perez, G. Moloney, E. Morelli, E. Morillas, R. O'Connor, J.S. Cruz-Pereira, V. L. Peterson, K. Rea, N.L. Ritz, E. Sherwin, S. Spichak, E.M. Teichman, M van de Wouw, A.P. Ventura-Silva, S.E. Wallace-Fitzsimons, N. Hyland, G. Clarke, T. G. Dinan, The microbiota-gut-brain Axis, Physiol. Rev. 99 (4) (2019) 1877–2013.
[130] J. Humann, B. Mann, G. Gao, P. Moresco, J. Ramahi, L.N. Loh, A. Farr, Y. Hu, K. Durick-Eder, S.A. Fillon, R.J. Smeyne, E.I. Tuomanen, Bacterial peptidoglycan traverses the placenta to induce fetal neuroproliferation and aberrant postnatal behavior, Cell Host Microbe 19 (6) (2016) 901.
[131] A. Ait-Belgnaoui, A. Colom, V. Braniste, L. Ramalho, A. Marrot, C. Cartier, E. Houdeau, V. Theodorou, T. Tompkins, Probiotic gut effect prevents the chronic psychological stress-induced brain activity abnormality in mice, Neuro Gastroenterol. Motil. 26 (4) (2014) 510–520.
[132] F. Guida, F. Turco, M. Iannotta, D. De Gregorio, I. Palumbo, G. Sarnelli, A. Furiano, F. Napolitano, S. Boccella, L. Luongo, M. Mazzitelli, A. Usiello, F. De Filippis, F.A. Iannotti, F. Piscitelli, D. Ercolini, V. de Novellis, V. Di Marzo, R. Cuomo, S. Maione, Antibiotic-induced microbiota perturbation causes gut endocannabinoidome changes, hippocampal neuroglial reorganization and depression in mice, Brain Behav. Immun. 67 (2018) 230–245.
[133] J. Pearson-Leary, C. Zhao, K. Bittinger, D. Eacret, S. Luz, A.S. Vigderman, G. Dayanim, S. Bhatnagar, The gut microbiome regulates the increases in depressive-type behaviors and in inflammatory processes in the ventral hippocampus of stress vulnerable rats, Mol Psychiatry 25 (5) (2020) 1068–1079.
[134] E.S. Ogbonnaya, G. Clarke, F. Shanahan, T.G. Dinan, J.F. Cryan, O.F. O'Leary, Adult hippocampal neurogenesis is regulated by the microbiome, Biol. Psychiatry 78 (4) (2015) e7–e9.
[135] S.E. Walsh, J.Y. Maillard, A.D. Russell, C.E. Catrenich, D.L. Charbonneau, R.G. Bartolo, Development of bacterial resistance to several biocides and effects on antibiotic susceptibility, J. Hosp. Infect. 55 (2) (2003) 98–107.
[136] S. Mostafa, B.J. Miller, Antibiotic-associated psychosis during treatment of urinary tract infections: a systematic review, J. Clin. Psychopharmacol. 34 (4) (2014) 483–490.
[137] L. Mohle, D. Mattei, M.M. Heimesaat, S. Bereswill, A. Fischer, M. Alutis, T. French, D. Hambardzumyan, P. Matzinger, I.R. Dunay, S.A. Wolf, Ly6C(hi) monocytes provide a link between antibiotic-induced changes in gut microbiota and adult hippocampal neurogenesis, Cell Rep. 15 (9) (2016) 1945–1956.
[138] P. van Baarlen, J.M. Wells, M. Kleerebezem, Regulation of intestinal homeostasis and immunity with probiotic lactobacilli, Trends Immunol. 34 (5) (2013) 208–215.
[139] R. Ishikawa, H. Fukushima, Y. Nakakita, H. Kado, S. Kida, Dietary heat-killed Lactobacillus brevis SBC8803 (SBL88) improves hippocampus-dependent memory performance and adult hippocampal neurogenesis, Neuropsychopharmacol Rep 39 (2) (2019) 140–145.
[140] C. Bjorkholm, L.M. Monteggia, Bdnf - a key transducer of antidepressant effects, Neuropharmacology 102 (2016) 72–79.
[141] O.F. O'Leary, E.S. Ogbonnaya, D. Felice, B.R. Levone, L. Cc, P. Fitzgerald, J.A. Bravo, P. Forsythe, J. Bienenstock, T.G. Dinan, J.F. Cryan, The vagus nerve modulates BDNF expression and neurogenesis in the hippocampus, Eur. Neuropsychopharmacol. 28 (2) (2018) 307–316.
[142] H.H. Lin, M.C. Kuang, I. Hossain, Y. Xuan, L. Beebe, A.K. Shepherd, M. Rolandi, J.W. Wang, A nutrient-specific gut hormone arbitrates between courtship and feeding, Nature 602 (7898) (2022) 632–638.
[143] P. Kundu, E. Blacher, E. Elinav, S. Pettersson, Our gut microbiome: the evolving inner self, CELL 171 (7) (2017) 1481–1493.
[144] P. Kundu, H.U. Lee, I. Garcia-Perez, E.X.Y. Tay, H. Kim, L.E. Faylon, K.A. Martin, R. Purbojati, D.I. Drautz-Moses, S. Ghosh, J.K. Nicholson, S. Schuster, E. Holmes, S. Pettersson, Neurogenesis and prolongevity signaling in young germ-free mice transplanted with the gut microbiota of old mice, Sci. Transl. Med. 11 (518) (2019).
[145] C.B. Rodríguez-Moreno, H. Cañeque-Rufo, M. Flor-García, J. Terreros-Roncal, E.P. Moreno-Jiménez, N. Pallas-Bazarra, C. Bressa, M. Larrosa, F. Cafini, M. Llorens-Martín, Azithromycin preserves adult hippocampal neurogenesis and behavior in a mouse model of sepsis, Brain Behav. Immun. 117 (2024) 135–148.
[146] A. Wimo, L. Jönsson, J. Bond, M. Prince, B. Winblad, The worldwide economic impact of dementia 2010, Alzheimers Dement 9 (1) (2013) 1–11.e13.
[147] H.L. Pedersen, K.D. Horvei, D. Thiyagarajan, G.E. Norby, N. Seredkina, G. Moroni, G.O. Eilertsen, H. Holdaas, E.H. Strom, G. Bakland, P.-L. Meroni, O. P. Rekvig, Lupus nephritis: low urinary DNase I levels reflect loss of renal DNase I and may be utilized as a biomarker of disease progression, Journal of Pathology Clinical Research 4 (3) (2018) 193–203.