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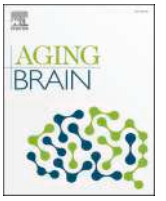

Invited Opinion

Human adult hippocampal neurogenesis in health and disease

MC. Alonso-Moreno [a,b,c,1], M. Gallardo-Caballero [a,b,c,1], AV. Prádanos-Senén [a,c,1], M. Llorens-Martín [a,b,c,*]

[a] Department of Molecular Neuropathology, Centro de Biología Molecular "Severo Ochoa" (CBMSO), Spanish Research Council (CSIC)–Universidad Autónoma de Madrid (UAM), Madrid, Spain
[b] Center for Networked Biomedical Research On Neurodegenerative Diseases (CIBERNED), Madrid, Spain
[c] Department of Molecular Biology, Faculty of Sciences, Universidad Autónoma de Madrid, Madrid, Spain

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ABSTRACT

The mammalian hippocampus generates new dentate granule cells (DGCs) throughout life. This process, named adult hippocampal neurogenesis (AHN), participates in hippocampal functions such as memory and mood regulation. Moreover, AHN is impaired in mouse models and patients with neurodegenerative and psychiatric disorders. Additionally, physiological aging targets AHN and the integrity of the hippocampal neurogenic niche. This perspective review aims to discuss the regulation of human AHN in patients with neurodegenerative and psychistric conditions. Moreover, we will address key adaptations of human AHN and the neurogenic niche in response to physiological aging.

Introduction

The mammalian hippocampus has a remarkable capacity to generate new neurons, namely dentate granule cells (DGCs), throughout life [4]. This process, known as adult hippocampal neurogenesis (AHN), supports enhanced hippocampal neural plasticity during aging. Moreover, it is involved in key hippocampal functions, such as learning and memory, and mood regulation (reviewed in [41]. In particular, AHN participates in pattern separation [107], spatial memory [75], forgetting of established memories [1], as well as depressive- and anxiety-like behaviors [68]. To support the continuous generation of new neurons, the inner border of the dentate gyrus (DG), which is in tight contact with the hilus, is composed of a specialized matrix, named the neurogenic niche. This niche is enriched in a profuse vascular network, astrocytes, microglia, and immature neurons [132]. This unique environment orchestrates complex crosstalk to regulate AHN in mammals [114,121,127].

Within this matrix, a resident population of neural stem cells (NSCs) with radial-glia-like properties [112]occasionally divides and gives rise to transit-amplifying progenitors and neuroblasts [76]. These cells are characterized by high proliferative capacity and commitment to the neuronal lineage. After exiting the cell cycle, neuroblasts differentiate into immature neurons, which express the microtubule-associated protein Doublecortin (DCX) and the extracellular matrix Polysialylated-neural cell adhesion molecule (PSA-NCAM), among other markers (Fig. 1) [27,103]. Immature neurons go through distinct maturation stages before becoming (almost) [37] indistinguishable from their developmentally generated fully mature counterparts [76]. During the aforementioned

* Corresponding author at: Centro de Biología Molecular "Severo Ochoa", Spanish Research Council (CSIC), Universidad Autónoma de Madrid (campus de Cantoblanco), c/Nicolás Cabrera 1, 28049 Madrid, Spain.
E-mail address: m.llorens@csic.es (M. Llorens-Martín).
[1] Contributed equally.

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differentiation stages, newborn DGCs become functionally integrated into the hippocampal trisynaptic circuits [146]. This integration process involves the establishment of afferent synaptic contacts from both excitatory and inhibitory sources of innervation [59,96,146]. Moreover, newborn DGCs send their axonal projections toward their synaptic targets in the CA2 and CA3 hippocampal subfields [82,146]. In parallel, immature neurons migrate from the subgranular zone (SGZ) towards the granule cell layer (GCL) [76] and acquire a progressively more complex characteristic Y-shape morphology, which might be related to their physiological functions (reviewed in [83].

Despite the consistent occurrence of AHN across mammalian phylogeny, this process presents species-specific particularities (revised in [126]. In this regard, the occurrence of AHN in humans was first shown by Eriksson et al. in 1998 [48]. Subsequently, although a small number of studies did not find evidence of human AHN [34,52,115], most overwhelmingly support the occurrence of this phenomenon during physiological and pathological aging [21,24,51,77,97,116,127,128,129,147]. In this context, although most of the available literature is based on immunohistochemistry (IHC), recent single-cell RNA-seq (sc-RNAseq) studies are starting to unveil the complex molecular landscape underlying human AHN and its regulation [129,147]. In this respect, both physiological aging and pathological conditions have a dramatic impact on AHN and the homeostasis of the hippocampal neurogenic niche (Table 1), as further discussed in the forthcoming sections of this review. We will focus on the key aspects that characterize human AHN, as well as the current understanding of its regulation during physiological and pathological aging. In particular, we will summarize available evidence of AHN impairments in aged individuals, as well as in patients with distinct neurodegenerative and psychiatric disorders. We will also address some limitations inherent to human studies and outline future directions and current challenges in the field of human AHN research.

Human adult hippocampal neurogenesis during physiological aging

As mentioned above, AHN was first observed in humans in a study conducted by Eriksson et al., in which they detected Bromodeoxyuridine $(BrdU)^+$ / Neuronal Nuclei $(NeuN)^+$ cells in the DG of patients previously administered BrdU, a thymidine analog used for labeling proliferating cells [48]. A subsequent study in 2014 corroborated these findings, identifying 5-iodo-2′-deoxyuridine $(IdU)^+$ neurons in the hippocampal DG of cancer patients treated with this compound [49]. A large and growing body of literature has explored the occurrence of AHN in humans using other techniques. For instance, Manganas et al. employed an *in vivo* method to find metabolites specific to NSCs and progenitor cells, identifying a lipid signal at 1.28 ppm as a biomarker detected by functional magnetic spectroscopy in the human brain [90]. Furthermore, using a ^{14}C birth-dating method [16] and mathematical models, Spalding et al. estimated that roughly 700 new neurons are generated daily in the human DG [116]. However, most studies have relied on immunohistochemical markers to study AHN. NSCs and progenitor cells have been consistently observed in the hippocampus, as evidenced by the presence of $Nestin^+$ and SRY-box transcription factor 2 $(Sox2)^+$ cells [21,22,24,28,77,79,127]. Moreover, a population of radial glial-like (RGL) cells that were $Nestin^+$, $Sox2^+$, $Vimentin^+$ and glial fibrillary acidic protein $(GFAP)^+$ while lacking S100 calcium-binding protein B (S100β) expression was identified in the human DG [127]. Additionally, cell proliferation markers, including -Phospho-Histone H3 (PH3) [86,127], Ki67 [18,21,22,24,77,79,92], and minichromosome maintenance complex component 2 (MCM2) [34,77,86] were also identified, suggesting active cell division. Moreover, proliferative neuroblast markers, such as human neuronal proteins C and D (HuC/HuD), further corroborated the commitment of proliferative cells to the neuronal lineage [127].

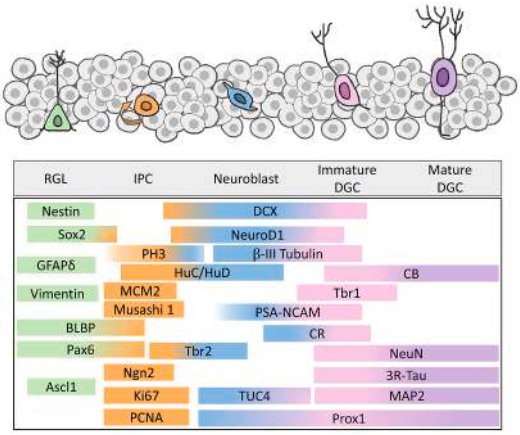

Fig. 1. Schematic diagram showing the main stages encompassed by human adult hippocampal neurogenesis. RGL: Radial glia-like cell. IPC: Intermediate progenitor cell. DGC: Dentate granule cell. Sox2: SRY-box transcription factor 2. GFAP: glial fibrillary acidic protein. BLBP: Brain lipid-binding protein. Pax6: Paired box 6. Ascl1: Achaete-Scute family BHLH transcription factor 1. PH3: Phospho-Histone H3. HuC/HuD: Human neuronal proteins C and D. MCM2: Minichromosome maintenance complex component 2. Tbr: T-box brain protein. Ngn2: Neurogenin 2. PCNA: Proliferating cell nuclear antigen. DCX: Doublecortin. PSA-NCAM: Polysialylated-neural cell adhesion molecule. CR: Calretinin. TUC4: Turned On After Division/Ulip/ CRMP-4. CB: Calbindin. NeuN: Neuronal Nuclei. MAP2: Microtubule-associated protein 2. 3R-Tau: Three-repeated Tau. Prox1: Prospero Homeobox 1.

Table 1
Impact of physiological aging and pathological conditions on adult hippocampal neurogenesis and the neurogenic niche. NSCs: Neural stem cells. DGCs: Dentate granule cells. AD: Alzheimer's disease. PD: Parkinson's disease. LBD: Dementia with Lewy bodies. HD: Huntington's disease. ALS: Amyotrophic lateral sclerosis. FTD: Frontotemporal dementia. CJD: Creutzfeldt Jakob disease. MD: Major depression. SCH: Schizophrenia. BD: Bipolar disorder. SSRIs: Selective serotonin reuptake inhibitors. TCAs: Tricyclic antidepressants. Sox2: SRY-box transcription factor 2. GFAP: glial fibrillary acidic protein. S100β: S100 calcium-binding protein B. PCNA: Proliferating cell nuclear antigen. HuC/HuD: Human neuronal proteins C and D. MCM2: Minichromosome maintenance complex component 2. PH3: Phospho-Histone H3. NPCs: Neural progenitor cells. Top2a: DNA Topoisomerase II Alpha. Egfr: Epidermal growth factor receptor. PSA-NCAM: Polysialylated-neural cell adhesion molecule. DCX: Doublecortin. CR: Calretinin. Prox1: Prospero Homeobox 1. MAP2: Microtubule-associated protein 2. CB: Calbindin. NeuN: Neuronal Nuclei. DG: Dentate gyrus. PAS: Periodic acid–Schiff.

		Physiological aging	Neurodegenerative diseases	Neuropsychyatric diseases
Adult hippocampal neurogenesis	**NSCs**	= Nestin$^+$ cells [21,127], = Sox2$^+$ cells [79,127], ↓ Sox2$^+$ cells [21], = GFAPδ$^+$ cells [92]	**AD:** ↓ Sox2 reactivity [39], ↑ Nestin reactivity and ↓ Musashi-1 reactivity [101]; = Sox2$^+$ cells [55], ↓ Nestin$^+$ cells and = Nestin$^+$GFAP$^-$ cells [31] **PD:** ↓ Nestin$^+$ cells [69], ↑ Nestin$^+$S100β$^-$ cells and ↑ Sox2$^+$ cells [127] **LBD:** ↓ Musashi-1$^+$ cells [72], ↓ Sox2$^+$ cells [139], = Nestin$^+$S100β$^-$ cells and = Sox2$^+$ cells [127] **HD:** ↑ Nestin$^+$S100β$^-$ cells [127] **ALS:** ↓ GFAPδ$^+$ cells [53,56], ↑ Nestin$^+$S100β$^-$ cells and ↑ Sox2$^+$ cells [127] **FTD-ALS:** ↓ GFAPδ$^+$ cells [53,56] **FTD:** = Nestin$^+$S100β$^-$ cells [127] **CJD:** = Sox2$^+$ cells [55]	**MD:** = Nestin$^+$ cells [20], ↑ Nestin$^+$ cells in patients treated with SSRIs and TCAs [22,24] **Addiction:** = Nestin$^+$ cells and ↓ Musashi-1$^+$ cells in heroin addicts [11], ↓ Sox2$^+$ cells in alcoholics [79]
	Proliferation	= Ki67$^+$ cells [21], ↓ Ki67$^+$ cells [42,79,92], = PH3$^+$ cells [127], = PCNA$^+$ cells [94], ↓ NPCs (marked by MKi67, Top2a and Egfr) [85]	**AD:** = Ki67$^+$ cells [19], ↑ Ki67$^+$ cells [55], ↓ PCNA$^+$ cells [128] **PD:** ↑ PH3$^+$ cells [127] **LBD:** ↑ PCNA$^+$ cells [72], = PH3$^+$ cells [127] **HD:** = PCNA$^+$ cells [84], = PH3$^+$ cells [127] **ALS:** ↓ PCNA$^+$ cells and ↓ Ki67$^+$ cells [53,56], = PH3$^+$ [127] **FTD-ALS:** ↓ PCNA$^+$ cells and ↓ Ki67$^+$ cells [53,56] **CJD:** ↑ Ki67$^+$ cells [55]	**MD:** = Ki67$^+$ cells [20,24,106], ↑ Ki67$^+$ cells in patients treated with TCAs [24], ↓ Mcm2$^+$ cells and = PH3$^+$ cells [86], = PCNA$^+$ cells [134] **SCH:** ↓ Ki67$^+$ cells [2,106], = PCNA$^+$ cells [134] **BD:** = Ki67$^+$ cells [106], = PCNA$^+$ cells [134] **Addiction:** = Ki67$^+$ cells in heroin addicts [11], ↓ Ki67$^+$ cells in alcoholics [79]
	Neuroblasts	= HuC/HuD$^+$ cells [127]	**AD:** ↓ HuC/HuD$^+$ cells [46] **PD:** ↑ HuC/HuD$^+$ cells [127] **LBD:** = HuC/HuD$^+$ cells [127] **HD:** = HuC/HuD$^+$ cells [127]	

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Table 1 (*continued*)

	Physiological aging	Neurodegenerative diseases	Neuropsychyatric diseases
		ALS: = HuC/HuD$^+$ cells [127] **FTD:** ↓ HuC/HuD$^+$ cells [127]	
Immature neurons (early differentiation)	↓ PSA-NCAM$^+$ cells [21], ↓ DCX$^+$ cells [34,77,92,97,127], ↓ STMN1, STMN2, DCX [135]	**AD:** ↑ DCX expression [71], ↑ PSA-NCAM reactivity, = DCX reactivity and β-III-tub reactivity [101], ↑ CR$^+$ cells [55], ↓ DCX$^+$ cells [31,39]; Lazarov O et al., 2024; [97,128,147], ↓ DCX$^+$PSA-NCAM$^+$ cells and ↓ DCX$^+$β-III-tub$^+$ cells [97], ↓ DCX$^+$CR$^-$ cells, ↓ DCX$^+$CR$^+$ cells and ↓ CR$^+$Prox1$^+$ cells [31] **PD:** ↓ β-III-tub$^+$ cells [69], ↑ DCX$^+$ cells [127], ↓ DCX$^+$ cells [102] **LBD:** = DCX$^+$ cells [72], = DCX$^+$ cells [127] **HD:** ↑ PSA-NCAM$^+$ cells and ↑ DCX$^+$ cells [127] **ALS:** ↓ PSA-NCAM$^+$ cells [53,56], ↑ DCX$^+$ cells [127] **FTD-ALS:** ↓ PSA-NCAM$^+$ cells [53,56] **FTD:** ↓ DCX$^+$CR$^+$ cells and = DCX$^+$ cells [127] **CJD:** ↑ CR$^+$ cells [55]	**MD:** = CR$^+$ cells [145], = CR expression [134], ↑ DCX$^+$ cells in patients without psychosis compared to those with psychosis [47] **SCH:** = CR$^+$ cells [145], ↑ CR expression [134] **BD:** = CR$^+$ cells [145], ↑ CR expression [134] **Addiction:** ↓ DCX$^+$ cells in alcoholics [79]
Immature neurons (late differentiation)		**AD:** ↓ Map2a and b isoforms [80], ↓ DCX$^+$CB$^+$ cells, ↓ DCX$^+$NeuN$^+$ cells, ↓ DCX$^+$Prox1$^+$ cells [97] **PD:** ↓ DCX$^+$NeuN$^+$ cells [127], = DCX$^+$NeuN + cells [102] **LBD:** DCX$^+$NeuN$^+$ cells [127] **HD:** ↓ DCX$^+$NeuN$^+$ cells [127] **FTD:** ↓ DCX$^+$NeuN$^+$ cells [127]	
Total DGCs	= DAPI with neuronal nuclear morphology [127]	**PD:** = DAPI with neuronal nuclear morphology [127], = NeuN$^+$ cells [102] **LBD:** = DAPI with neuronal nuclear morphology [127] **HD:** ↑ DAPI with neuronal nuclear morphology [127] **ALS:** = DAPI with neuronal nuclear morphology [127] **FTD:** = DAPI with neuronal	**MD:** ↑ dentate granule cells identified by Nissl staining [117], = CB expression [134], = dentate granule cells identified by Nissl staining [35], ↓ NeuN$^+$ cells in anterior and mid DG [23], **SCH:** = neurons identified by Nissl staining in the hippocampus [66], ↓ CB mRNA expression in mid DG [3], = CB expression [134], = dentate granule cells identified by Nissl staining in anterior + posterior DG [50]

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Table 1 (*continued*)

		Physiological aging	Neurodegenerative diseases	Neuropsychyatric diseases
			nuclear morphology [127]	**BD:** = CB expression [134] **Addiction:** ↓ dentate granule cells identified by cresyl-violet, PAS, or hematoxylin-eosin staining in alcoholics [14], ↓ NeuN$^+$ cells in alcoholics [43]
Neurogenic niche	**Microglia**	↑ %CD83$^+$ Iba1$^+$ cells among Iba1$^+$ cells [119], = Iba1$^+$ cells [127], ↓ phagocytic pouches per Iba1$^+$ microglia [127], = glial cells identified by Nissl staining [21]	**AD:** ↑ Iba1$^+$ cells at Braak-Tau stages III-IV [46], distrophyc morphology in Iba1$^+$ cells [108], = Iba1$^+$ cells (Lazarov O et al., 2024) **PD:** ↓ phagocytic pouches [127] **LBD:** ↓ phagocytic index [127] **HD:** ↓ phagocytic index [127] **ALS:** ↓ phagocytic pouches [127] **FTD:** = phagocytic index [127]	**MD:** ↑ glial cells identified by Nissl staining [117], = glial cells identified by Nissl staining [35] **Addiction:** microgliosis [136]
	Astrocytes	= S100β$^+$ cells [127], ↑ GFAP expression and = S100β$^+$ cells (↑ astrocyte activation) [92], ↑ % GFAP$^+$ S100β $^+$ cells among S100β $^+$ cells [119], = glial cells identified by Nissl staining [21]	**AD:** ↑ GFAP expression [19], ↑ GFAP$^+$ cells at Braak-Tau stages V-VI [46], ↑ Nestin$^+$GFAP$^+$ [31], = GFAP$^+$ cells (Lazarov O et al., 2024) **PD:** ↑ S100β$^+$ cells [127] **LBD:** = S100β$^+$ cells [127] **HD:** ↑ S100β$^+$ cells [127] **ALS:** ↑ S100β$^+$ cells [127] **FTD:** ↑ S100β$^+$ cells [127]	**MD:** ↑ glial cells identified by Nissl staining [117], = glial cells identified by Nissl staining [35] **Addiction:** astrocytosis [136]
	Vasculature	= capillary density [127], = DG capillary thickness [127], ↓ Nestin$^+$ capillary density [21]; ↓ Nestin$^+$ capillary area density [21], ↓ Nestin$^+$ capillary length density [21]	**AD:** ↑ Ki67$^+$ cells in VWF$^+$ vessels [19] **PD:** = capillary thickness [127] **LBD:** ↑ capillary thickness [127] **HD:** ↑ capillary thickness [127] **ALS:** = capillary thickness [127] **FTD:** ↑ capillary thickness [127]	**MD:** ↑ capillary area in patients treated with SSRIs [22]

However, a study conducted by Cipriani et al. did not find evidence of the proliferative activity of Nestin$^+$ cells using Ki67 labeling [34]. Additionally, recent studies using sc-RNAseq have identified cells that express neural progenitor cell (NPC) markers [32] and neuroblast-like populations [141], thereby further supporting the persistence of neurogenesis in the adult hippocampus. Proliferation markers shed light on the early stages of neurogenesis. To track the maturation of newly generated neurons, numerous studies used DCX and PSA-NCAM, providing compelling evidence of immature neurons and strongly supporting the notion of ongoing AHN in humans. For instance, an early study by Knoth et al. detected the presence of DCX$^+$ neurons in humans from 1 day to 100 years old [77]. Moreover, Liu et al. detected DCX$^+$ cells using immunofluorescence and Western blot methods [81]. In contrast, several authors reported undetectable expression of DCX in human adults [42,111,115]. However, numerous subsequent studies consistently demonstrated the presence of DCX$^+$ and PSAN-CAM$^+$ immature neurons in the adult human DG [21,79,92,97,124,127,128]. Additionally, DCX co-localizes with neuronal markers of distinct maturation stages, including Calretinin (CR) (early) and Calbindin (CB) (advanced) [97,127]. Therefore, there is a considerable body of evidence confirming the presence of maturing neurons in the human

hippocampus, with contrasting findings largely attributable to variations in experimental protocols, as previously reviewed [126]. Moreover, recent sc-RNAseq data have been used to reconstruct the full cellular trajectory of AHN, thereby highlighting the heterogeneity of progenitors and immature DGCs [8,60,85,135,147]. Additionally, new neurogenic markers enriched in humans have been validated, including ETNPPL [135,143], as well as STMN1 and STMN2 [135,147]. Interestingly, some studies found no transcriptomic signatures of AHN in the human hippocampus [52]. However, various methodological and computational challenges, such as sequencing depth, sample size, and processing, may influence the profiling of AHN using sc-RNAseq technologies [129].

It is now well established that AHN is modulated by distinct factors, including physiological aging. Research shows that the number of DCX^+ [34,77,92,97,127] and $PSA\text{-}NCAM^+$ [21] immature neurons decreases with age. In contrast, the number of cells positive for NSC markers [21,79,92,127], $Ki67^+$ proliferative cells [21], proliferating cell nuclear antigen $(PCNA)^+$ [94], $PH3^+$, HuC/HuD^+ [127] cells, and total DGCs [21,127] remain stable throughout aging. Consequently, it has been proposed that physiological aging selectively impacts certain maturation stages [92,127]. However, other authors have reported a decrease in $Sox2^+$ [21], and $Ki67^+$ [42,79,92] cells with aging. sc-RNAseq studies have also revealed significant age-related changes in the gene expression profiles of immature DGCs [147], a decline in cells expressing NSC markers and immature neurons [135], and a reduction of NPC marker-expressing cells [85] during physiological aging.

These age-related alterations in neural progenitor populations and immature neurons highlight the impact of aging on AHN. However, AHN does not occur in isolation. The neurogenic niche contributes to the regulation of this neurogenic process and is similarly targeted by aging. Astrocytes, a key component of the neurogenic niche, also undergo age-related changes and show regional heterogeneity. Boldrini et al. observed a ubiquitous distribution of mature astrocytes across the hilus and hippocampal formation [24], while Terreros-Roncal et al., reported an abundant presence of $S100\beta^+$ astrocytes in the DG [127]. Within the hippocampus, astrocytes show distinct subtypes based on location, morphology, and molecular profiles. These subtypes are often layer-specific, with molecular and morphological differences that are partially preserved in humans [74], while others contribute to functions such as synaptic modulation and injury response [8,119]. Several studies showed that aging stimulates astrocyte activation, while progenitor-like astrocytes ($Sox2^+$) decrease with age [92,119], although no correlation between age and $Sox2^+$ astrocytes was found in Terreros-Roncal et al. [127]. Similarly, microglia also show diverse subpopulations in the hippocampal neurogenic niche with specific molecular signatures that change over time [119]. Additionally, microglia with phagocytic pouches have polarized, highly ramified structures, in contrast to those without pouches. These structural differences are thought to be associated with variations in their phagocytic capacity [127]. Other studies reported clusters of homeostatic and pre-active microglia potentially influencing neurogenesis [8], as well as a specific microglial subtype (PCDH9high) that has a proinflammatory profile and interacts with neurons through specific ligand-receptor pathways [32]. Similar to astrocytes, microglia also undergo significant changes with age, shifting towards a reduction of their phagocytic capacity [127]. Interestingly, while aging leads to a decrease in microglial populations associated with inflammation and autophagy [119], there is also an increase in microglial activation [105,135] and reactive microglial proliferation [85]. Regarding oligodendrocytes, there are also multiple subtypes in the hippocampal niche, showing distinct gene expression patterns [8,119]. A decline in oligodendrocyte progenitor cells, suggesting reduced oligodendrogenesis, was observed with aging [119]. However, this finding contradicts the observation of enhanced oligodendrogenesis [105]. Moreover, previous research has established that approximately 7 % of the hippocampal GCL comprises blood vessels and capillaries [127], which are located near $Nestin^+$ cells, suggesting a role in supporting NSC growth and maturation [21,22,24]. While Boldrini et al. reported reduced capillary density with aging [21], this was not observed by Terreros-Roncal et al. [127]. Beyond the individual changes observed in each cellular population of the neurogenic niche, it is important to note that aging also influences the interactions between immature DGCs and other cell types located in their neighboring neurogenic niche [147].

Thus, taken together, these findings suggest that physiological aging disrupts AHN by altering both cells belonging to the neurogenic lineage and the homeostasis of the neurogenic niche. These age-related changes might contribute to a decline in neurogenesis, which may ultimately impair hippocampal function and cognitive processes. The precise mechanisms underlying the age-related decline in AHN, as well as the specific effects of neurogenic niche alterations on cognition and behavior, remain poorly understood, thereby highlighting the need for additional mechanistic studies to explore the impact of these changes on hippocampal function.

AHN in patients with neurodegenerative diseases

Neurodegenerative diseases comprise a spectrum of disorders primarily characterized by the loss of neurons and synapses in the central or peripheral nervous system, leading to the impairment of memory, cognition, behavior, and sensory and motor function [138]. According to the World Health Organization (WHO), over 50 million people worldwide are affected by these conditions, and their incidence is expected to rise exponentially in the coming years due to the increasing number of elderly people, thus posing a major global challenge.

AHN and Alzheimer's disease

Alzheimer's disease (AD), the most prevalent neurodegenerative disease, is histopathologically characterized by the deposition of β-amyloid plaques and neurofibrillary tangles of hyperphosphorylated tau protein in the hippocampal region [25]. The way in which AHN is affected in AD has been a subject of debate, probably due to the intrinsic limitations of working with human tissue [126].

For instance, findings regarding the effects of AD on cells expressing NSC markers are inconsistent. While some studies reported decreased levels of Sox2 immunoreactivity [39] and a decreased proportion of $Nestin^+$ cells in the SGZ [31], others described either an

increase in Nestin immunoreactivity [101] or no significant changes in the number of $Sox2^+$ cells [55]. Similarly, findings on proliferative progenitors are contradictory. No changes were initially reported in presenile AD brains [19], whereas subsequent studies revealed decreased levels of cells positive for Musashi1 [101], an RNA-binding protein associated with NSC self-renewal, and reduced numbers of HuC/HuD^+ [46] and $PCNA^+$ [128] cells. In contrast, only one study described increased numbers of $Ki67^+$ cells [55]. The alterations reported on immature neurons are more consistent. While early studies suggested that they remain unchanged [101] or are increased in AD brains, either by quantifying the expression of DCX by Western blot [71] or by quantifying CR^+ immature neurons by IHC [55], most of the available literature discloses a drop in the number of DCX^+ cells during AD progression both by IHC [31,39,97,128] and sc-RNAseq [78,147]. Specifically, using a tightly controlled methodology [51], our group conducted a study on a cohort of 13 neurologically healthy control subjects and 45 patients with AD, who were distributed throughout the 6 neuropathological Braak-Tau stages. The results demonstrated that the density of DCX^+ immature neurons was sharply reduced from Braak stage I onwards [97]. Interestingly, the disease not only reduced the number of immature neurons but also presumably their functionality, as revealed by sc-RNAseq analysis [147]. Moreover, a study of microtubule-associated protein 2 (Map2) isoform expression [80] revealed a blockade in the maturation of newborn neurons, which was also confirmed by a reduction in the expression of PSA-NCAM, Prospero Homeobox 1 (Prox1), β-III-tub, NeuN, and CB in DCX^+ immature neurons, starting at Braak-Tau stage III and throughout the subsequent stages of the disease [31,97]. The molecular pathways underlying the alterations in AHN have been linked to Notch and BMP signaling [31], specifically to the BMP6 factor [39].

However, understanding the disruptions in the neurogenic process requires exploration of the broader neurogenic niche. In this context, one semi-quantitative study reported increased glial fibrillary acidic protein (GFAP) expression in the SGZ of AD brains [19]. A subsequent study described a decrease in the numbers of $GFAP^+$ cells at Braak-Tau stages III-IV, compared to Braak-Tau stages 0-II, followed by an increase at Braak-Tau stages V-VI [46]. However, this study lacked a control group without neurofibrillary tangle pathology. Regarding microglia, the same study reported an increased number of $Iba1^+$ cells at Braak-Tau stages III-IV compared to the other stages [46] and these cells were also observed to have a dystrophic morphology [108]. In contrast, recent sc-RNAseq studies have not detected changes in astrocyte or microglia densities [78], but have revealed dysregulation of the expression of genes related to synapses, cell adhesion, and signal transduction [93,119]. Concerning blood vessels, increased proliferation of Von Willebrand Factor $(VWF)^+$ endothelial cells was reported [19], along with alterations in the interaction between blood vessels and NSCs [34].

Overall, the evidence discussed above indicates that AHN is significantly impaired in patients with AD, not merely as a consequence of the disease, but potentially contributing to its pathogenesis. In mice, the axons from the lateral entorhinal cortex (LEC) are the main afferent connections to newborn DGCs. A failure in AHN could compromise the structural and functional integrity of the axonal terminal, leading to retrograde degeneration of LEC neurons [144]. Such degeneration may underlie not only the hallmark memory and cognitive deficits of AD but also mood-related disorders, such as depression and anxiety. Moreover, a study reporting preserved neurogenesis in a subset of AD patients who remained cognitively intact [28] underscored the importance of AHN as a potential therapeutic target. However, there are still missing pieces in this puzzle that need to be addressed. Further studies are required to comprehensively assess the homeostasis of the neurogenic niche during disease progression. Comparative studies including both healthy controls and individuals at distinct Braak-Tau stages are essential to clarify how interactions between NSCs, glial cells, interneurons, and vascular components evolve during AD progression. Addressing these gaps will be crucial for developing a more integrative understanding of neurogenesis in AD.

AHN and α-synucleinopathies

α-synucleinopathies are a group of neurodegenerative disorders characterized by abnormal deposits of alpha-synuclein (α-syn) in neurons and glia, ultimately causing their death. The most common α-synucleinopathies are Parkinson's Disease (PD) and Lewy body dementia (LBD). In PD, there is a pronounced loss of dopaminergic neurons in the substantia nigra, whereas in LBD, α-syn aggregates accumulate in several cortical regions. Beyond motor dysfunction, both pathologies are characterized by cognitive impairment, visual hallucinations, and mood-related disorders [7,104].

Regarding the alteration of AHN in PD, several studies have reported contradicting results. While a decrease in the numbers of $Nestin^+$ cells was initially described [69], a later study found increased densities of $Nestin^+$ $S100\beta^-$ cells and HuC/HuD^+ proliferative cells [127]. Similarly, immature neurons were initially described to be reduced, as evidenced by decreased numbers of $\beta\text{-III-tub}^+$ cells [69] and DCX^+ cells [102]. In contrast, we revealed an increased density of DCX^+ cells [127]. Finally, while one study reported maintenance of the number of neurons in early ($NeuN^+$ DCX^+) and late ($NeuN^+$) maturation stages [102], our data unveiled a reduced expression of NeuN in DCX^+ cells [127]. Beyond these cellular discrepancies, the neurogenic niche is further compromised in PD, including altered microglial phagocytic capacity, marked astrogliosis, and thickened capillaries compared to controls [127].

Regarding LBD, some reports indicate a reduction in the number of $Musashi1^+$ [72] and $Sox2^+$ [139] cells, whereas our group observed an increased density of $Nestin^+$ $S100\beta^-$ cells [127]. Additionally, while proliferative $PCNA^+$ cells were described to be increased [72], our research did not reveal significant changes [127]. Notably, the number of immature neurons and neurons in later maturation stages appears to be unaffected by the disease [72,127]. Finally, the neurogenic niche is affected in patients with LBD, who show impaired microglial phagocytosis and increased capillary thickness [127].

Although the hippocampus is not the principal region affected in α-synucleinopathies, both PD and LBD show specific alterations in AHN. These neurogenic changes may contribute significantly to the cognitive deficits and mood disturbances experienced by patients, suggesting that targeting AHN could pave the way for innovative therapeutic strategies.

AHN in other neurodegenerative diseases

Huntington's disease (HD) results from an expanded CAG trinucleotide repeat in the gene encoding the protein huntingtin, which leads to its malfunctioning, fragmentation, and subsequent neuronal death. Consequently, patients develop motor impairments, chorea, and cognitive deficits [10]. Additionally, deficits in spatial memory and perception have been linked to hippocampal alterations [63], suggesting that the neurogenic process is potentially impaired. In this regard, a study on AHN in HD described that the number of $PCNA^+$ proliferative cells does not change [84], while $Nestin^+$ $S100\beta^-$ NSCs and DCX^+ immature neuron densities were both increased [127]. Notably, DCX^+ cells show morphological abnormalities, early maturation impairments, and reduced NeuN expression [127]. Furthermore, the niche homeostasis is altered in HD, as evidenced by the presence of astrogliosis, altered microglial phagocytosis, and thickened capillaries [127].

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder primarily affecting motor neurons. It is most commonly characterized by Transactive response DNA binding protein of 43 kDa (TDP-43) inclusions, although certain types also show superoxide dismutase type 1 (SOD1) aggregates. Beyond the hallmark motor dysfunction, nearly half of ALS patients experience cognitive and behavioral impairments, and 13 % of them develop frontotemporal dementia (FTD) [62]. Interestingly, hippocampal pathology has been observed in ALS patients [33], underscoring the importance of exploring AHN in this disease. In this context, some studies reported a reduction in the number of $GFAP\delta^+$ NSCs [53,56], whereas our group found increased densities of $Nestin^+$ $S100\beta^-$ NSCs [127]. Similarly, while Galán et al. and Gómez-Pinedo et al. documented decreased numbers of $PCNA^+$ and $Ki67^+$ proliferative cells, our findings revealed preserved densities of HuC/HuD^+ and $PH3^+$ proliferative cells [127]. Moreover, although reduced numbers of $PSA\text{-}NCAM^+$ immature neurons have been observed in ALS [53,56], our data indicate increased densities of DCX^+ immature neurons, albeit with altered morphology [127]. Finally, the neurogenic niche in ALS appears to be compromised, showing astrogliosis, diminished microglial phagocytic pouches, and thickened capillaries [127].

FTD is marked by the accumulation of protein aggregates, including fused in sarcoma (FUS) TDP-43 and Tau, in the temporal and frontal cortices, leading to impairments in executive functions, including behavioral regulation and language [6]. In some cases, hippocampal degeneration is also evident [123]. Therefore, the study of AHN is relevant in this pathology. Notably, the aforementioned studies by Galan et al. and Gomez-Pinedo et al. in patients with both ALS and FTD reported an even greater pronounced reduction in $GFAP\delta^+$ NSCs, $PCNA^+$ and $Ki67^+$ proliferative cells, and $PSA\text{-}NCAM^+$ immature neurons [53,56]. In contrast, our findings revealed no significant change in the density of $Nestin^+$ $S100\beta^-$ NSCs, a decrease in the density of proliferative HuC/HuD^+ cells, and stable densities of DCX^+ immature neurons [127]. Moreover, the neurogenic niche in FTD is disrupted, as evidenced by astrogliosis, thickened capillaries, and a tendency toward a reduced microglial phagocytic index [127].

Creutzfeldt Jakob disease (CJD) is a neurodegenerative disorder characterized by the accumulation of misfolded Prion Protein (PrPˆSc) in the cortex, basal ganglia, and cerebellum, ultimately leading to cognitive dysfunction, motor disorder, and behavioral abnormalities [99]. Notably, patients with CJD show an increase in the number of $Ki67^+$ proliferative cells, an unaltered number of $Sox2^+$ cells, and an increased number of CR^+ immature neurons [55]. However, the putative alteration of the neurogenic niche has not been addressed to date.

In conclusion, although the primary pathological features of HD, ALS, FTD, and CJD center on distinct molecular abnormalities and regional neurodegeneration, the evidence discussed suggests that disruptions in AHN and neurogenic niche homeostasis may represent a shared underlying mechanism contributing to the cognitive and behavioral deficits observed in these diseases. These findings not only deepen our understanding of the complex interplay between neurodegeneration and hippocampal plasticity but also point to AHN as a promising target for developing novel therapeutic strategies.

AHN in patients with neuropsychiatric conditions

According to the WHO, 970 million people worldwide, or 1 in every 8 people, live with a mental health condition. These conditions are characterized by significant disruptions in cognition, emotional regulation, or behavior, often leading to distress or impaired capacity to undertake routine daily tasks. As previously discussed, aging is a key factor negatively modulating AHN. Moreover, age-related reductions in neuroplasticity diminish the brain's resilience to stress, thereby increasing susceptibility to late-onset mood and anxiety disorders [73]. Although many neuropsychiatric conditions originate during early development, aging appears to exacerbate pre-existing vulnerabilities by further impairing neural plasticity and AHN. This positions AHN at a critical intersection between psychiatric pathophysiology and age-related cognitive decline. For example, in late-life, major depression (MD) is not only more prevalent but also strongly associated with hippocampal atrophy and cognitive decline [125], suggesting that aging and depression may converge on shared neurodegenerative pathways. Likewise, schizophrenia—despite its early onset—is characterized by progressive hippocampal volume loss that may reflect ongoing impairments in neurogenesis, contributing to the gradual worsening of cognitive and emotional dysfunction over the lifespan [148].

AHN and major depression

MD is a psychiatric disorder characterized by persistent low mood, low self-esteem, and restlessness [89]. Patients show not only affective but also cognitive symptoms, including alterations in executive functions, memory, learning, and concentration [64].

The detection of reduced hippocampal volume in patients with a history of depressive episodes was the first sign of a correlation between MD and hippocampal structural abnormalities [113]—a finding consistently reported in subsequent studies [30,36]. Furthermore, reduced hippocampal volume has been associated with lower rates of disease remission [38]. However, although

structural changes may be indicators of altered AHN and/or cell death, the specific changes in cellular populations contributing to these observations remain unclear. Moreover, stress has been reported to diminish the rate of AHN in mammals [29,57,58]. Notably, distinct antidepressants increase the rate of neurogenesis in rodents [40,45,87,88]. Furthermore, AHN is essential for the behavioral responses to antidepressants in mice [109]. In the context of these findings, the so-called adult neurogenesis hypothesis of depression proposed that abnormalities in the generation of new neurons have a causal relation with depressive behaviors [44,70].

Several studies have been performed in recent decades to unravel whether AHN is impaired in MD. An immunohistochemical study of post-mortem human hippocampal tissue showed no changes in $Ki67^+$ proliferating cells in the adult DG in patients with MD compared to controls [106]. Conversely, subsequent work showed a 50 % decrease in the number of $Ki67^+$ cells, though this was not statistically significant [24], as well as a decrease in $MCM2^+$ cells, and no change in $PH3^+$ proliferative cells [86] in MD patients. To assess alterations in the population of immature neurons, the expression of CR was quantified by IHC in the DG [134], which showed no changes in patients with MD. Another study reported an increased density of DCX^+ cells in depressed patients without psychosis compared to those with psychosis [47]. Moreover, untreated MD patients showed fewer $NeuN^+$ neurons in the anterior and mid-DG, which was coincident with a decreased GCL volume compared to controls [20,23]. Other work reported that total hippocampal volume and DGC density negatively correlates with disease duration [35]. Furthermore, glial cell density was found to be increased in MD patients [117].

Numerous studies have focused on whether antidepressant treatment affects AHN. In this regard, patients treated with either tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) showed an increased number of $Nestin^+$ cells [22,24]. Furthermore, patients receiving TCAs showed more $Ki67^+$ proliferative cells [24], whereas those treated with SSRIs presented an increased number of DGCs [23] compared to untreated patients. Notably, the alterations of the DG and GCL volume observed in untreated patients were counteracted in those treated with SSRIs [23], who also showed a larger area occupied by capillaries [22]. Moreover, neuron-derived extracellular vesicles from treatment-resistant patients were recently reported to contain lower levels of DCX, whereas an increase in DCX was observed after electroconvulsive therapy [140].

Most of the aforementioned studies suggest that MD targets AHN, although none of them depict all the individual stages of this neurogenic process. Moreover, antidepressant treatment seems to promote AHN. However, it remains to be determined whether such enhancement is required for the effects of such drugs in human beings.

AHN and schizophrenia

Schizophrenia (SCH) is a disabling neuropsychiatric disease with a complex neurobiological background. Patients present positive symptoms (e.g., hallucinations, delusions, or disorganization), negative symptoms (e.g., blunted affect, alogia, asociality, or anhedonia), and cognitive alterations, including hippocampal-dependent memory impairments [67,91].

SCH is associated with a bilateral reduction of hippocampal volume [98,130]. AHN dysfunction has been proposed as an underlying mechanism contributing to hippocampal atrophy. However, human post-mortem studies evaluating alterations of AHN in SCH are limited, and conclusive evidence supporting this hypothesis remains elusive. Quantification of $Ki67^+$ cells revealed decreased numbers of dividing cells in the DG [2,106], suggesting lower rates of proliferation in the hippocampus of SCH patients. The density of cells expressing the immature neuron marker PSA-NCAM was found to be reduced in the hilar region but not in other hippocampal subfields [9]. Despite densities of CR^+ cells remaining unchanged in the DG of SCH patients [145], increased protein expression was reported in a later study [134], suggesting that newborn neurons retain an upregulated expression of CR, thereby impeding full maturation. In line with this notion, mature neuronal marker CB mRNA was found to be decreased in the mid-DG [3]. Nonetheless, no changes in total cell number [50,66] or in CB protein expression [134] were detected in the post-mortem brains of SCH patients.

Although the aforementioned alterations point to dysregulated AHN in SCH, it remains unclear whether neurogenesis deficits affect a particular stage, as the specific targeting of individual AHN stages has not been elucidated to date. For instance, it has still to be determined whether changes in proliferation arise from an altered NSC population in SCH.

AHN and bipolar disorder

Bipolar disorder (BD) is a complex mental health condition characterized by unusual shifts in mood that last from days to several weeks, with euthymia—a normal, tranquil mental state—in between. It includes depressive periods, during which patients experience sadness or hopelessness, and manic/hypomanic periods characterized by abnormally elevated energy and irritability [110].

Studies examining hippocampal volume have been somewhat contradictory, with findings of similar [5,26], smaller [12,17], or larger [15,131] volumes in patients with BD. Nevertheless, *meta*-analysis studies showed that patients with BD exposed to lithium, a mood stabilizer used in the treatment of this condition, have larger hippocampal volumes, whereas those who had not been exposed to lithium have smaller ones compared to controls [61]. Despite the lack of solid evidence, such alterations have been suggested to reflect changes in AHN. Only a few human post-mortem studies have examined this relationship. Cell proliferation appears to be unaffected in BD, as revealed by the unchanged number of Ki67 + cells [106]. Similar to findings in SCH, elevated levels of CR expression were detected in the DG of BD patients compared to controls [134], although no alterations in the number of CR^+ cells were found in any hippocampal subregion [145]. Notably, no changes in the mature neuron marker CB were detected [134].

Some research has also linked the effects of lithium treatment to enhanced AHN. Although the mechanism of action of lithium is not yet clear, imaging studies showed that it accumulates in the hippocampus [118], and *in vitro* studies indicate that high-dose treatment leads to an increased number of neuroblasts, neurons, and glia [100]. Furthermore, in a study addressing the cellular phenotypes of neurons derived from induced pluripotent stem cells of BD patients, hyperexcitability of young neurons was observed, which was

selectively reversed only in patients who responded to lithium treatment [95].

Given the limited evidence available, it is challenging to draw conclusions about the relationship between AHN and BD. Studies investigating the full trajectories of AHN are needed to fully understand the effect of BD on AHN.

AHN and addiction

Available literature has proposed that the hippocampus is involved in drug-seeking and relapse [13,133]. Moreover, animal studies show that alcohol consumption and the administration of drugs of abuse result in altered AHN [54,65,122,142]. However, similar studies on the human brain are limited. Structural imaging research showed reduced hippocampal volume in alcoholics [120]. Additionally, stereological studies reported a reduction in the number of DGCs [14,43] and decreased numbers of $Ki67^+$, $Sox2^+$, and DCX^+ cells in the SGZ [79]. These findings suggest that neuron loss in alcohol abusers might be due to fewer cells being added to the DG, rather than from increased cell death. In heroin addicts, an increased expression of PSA-NCAM in the hilar region of the hippocampus, as well as astrocytosis and microgliosis, was observed [136,137]. Another study showed reduced numbers of Musashi-1^+ cells that co-expressed Nestin and GFAP but not NeuN or β-III-tub [11], thereby suggesting reduced numbers of precursor cells in heroin addicts. These findings point to alterations in the first stages of AHN in chronic drug abuse.

Therefore, while available evidence suggests impaired AHN in neuropsychiatric conditions, major gaps remain in understanding the exact nature and functional significance of such alterations in humans. Given the role played by the hippocampus in cognition, learning, and memory, failure of AHN would presumably impair these functions. Further research is needed to shed light on the relationship between AHN and mental illnesses, to identify the specific stages of AHN that are affected and to determine whether reduced AHN is a primary mechanism underlying hippocampal alterations or a secondary consequence of these disorders. Moreover, growing evidence suggests that, while psychiatric disorders may begin earlier in life, aging amplifies AHN deficits and worsens clinical outcomes, reinforcing the importance of contextualizing adult neurogenesis alterations within an aging framework.

Technical limitations

Progress in the human AHN field has been limited by the quality of available post-mortem brain samples. In this regard, technical aspects, such as the methodology used to preserve and process these samples, have a crucial effect on the experimental outcomes and the conclusions drawn from experimental observations (reviewed in [126]. Both ante- and post-mortem factors impact the suitability of a given human brain tissue for AHN research. For instance, prolonged hypoxic agonal states are related to a lowering of brain pH, a variable that is related to tissue, protein, and nucleic acid integrity. Moreover, prolonged post-mortem delay intervals may additionally contribute to protein degradation. And, even more importantly, the type of fixative used and a prolonged fixation time may lead to the lack of observation of AHN markers in human brain tissue, thereby leading to the erroneous conclusion that AHN is absent or inexistent. Therefore, one of the main limitations of human AHN studies is the lack of homogeneity in the quality and characteristics of human brain sample processing at distinct brain banks worldwide. In this regard, our group has dedicated a considerable efforts in recent years to provide the scientific community with a straightforward and reproducible experimental protocol suitable for the study of human AHN by IHC (reviewed in [51]. Moreover, other authors have performed much-needed systematic comparison analyses between the results obtained upon distinct experimental or analytic conditions in sc-RNAseq studies. Unsurprisingly, they found that slight variations in sample processing or the criteria applied during data analysis can substantially alter the conclusions of a given study [129]. Therefore, special attention should be devoted to conducting high-quality studies using systematic and reproducible methodologies to support the steady and rigorous advancement of the field.

Future directions

Once key technical aspects of human AHN studies have been clarified, the field will face a series of exciting challenges and novel questions that warrant further research. For instance, the timeframe required for a newborn neuron to fully develop in the human hippocampus (i.e., the duration of the differentiation stage of human AHN) remains to be elucidated. To address whether maturation time is lengthened, as occurs in other primate species, novel methodologies capable of providing higher temporal resolution are needed. Alternatively, methodologies with the potential to detect AHN *in vivo* [90] hold significant promise for unraveling the roles played by new neurons in the human brain. Last but not least, uncovering the causes and molecular triggers for AHN failure and/or the disruption of neurogenic niche homeostasis in distinct diseases will undoubtedly provide novel insights and pave the way toward new therapeutic avenues for as-yet incurable conditions such as AD.

CRediT authorship contribution statement

MC. Alonso-Moreno: Writing – review & editing, Writing – original draft. **M. Gallardo-Caballero:** Writing – review & editing, Writing – original draft. **AV. Prádanos-Senén:** Writing – review & editing, Writing – original draft. **M. Llorens-Martín:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

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.

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References

[1] Akers KG, Martinez-Canabal A, Restivo L, Yiu AP, De Cristofaro A, Hsiang HL, et al. Hippocampal neurogenesis regulates forgetting during adulthood and infancy. Science 2014;344:598–602.
[2] Allen KM, Fung SJ, Weickert CS. Cell proliferation is reduced in the hippocampus in schizophrenia. Aust N Z J Psychiatry 2016;50:473–80.
[3] Altar CA, Jurata LW, Charles V, Lemire A, Liu P, Bukhman Y, et al. Deficient hippocampal neuron expression of proteasome, ubiquitin, and mitochondrial genes in multiple schizophrenia cohorts. Biol Psychiatry 2005;58:85–96.
[4] Altman J. Autoradiographic investigation of cell proliferation in the brains of rats and cats. Anat Rec 1963;145:573–91.
[5] Altshuler LL, Bartzokis G, Grieder T, Curran J, Jimenez T, Leight K, et al. An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. Biol Psychiatry 2000;48:147–62.
[6] Antonioni A, Raho EM, Lopriore P, Pace AP, Latino RR, Assogna M, et al. Frontotemporal Dementia, where do we stand? International journal of molecular sciences: A Narrative Review; 2023. p. 24.
[7] Arnaoutoglou NA, O'Brien JT, Underwood BR. Dementia with Lewy bodies - from scientific knowledge to clinical insights. Nat Rev Neurol 2019;15:103–12.
[8] Ayhan F, Kulkarni A, Berto S, Sivaprakasam K, Douglas C, Lega BC, et al. Resolving cellular and molecular diversity along the hippocampal anterior-to-posterior axis in humans. Neuron 2021;109:2091–2105.e2096.
[9] Barbeau D, Liang JJ, Robitalille Y, Quirion R, Srivastava LK. Decreased expression of the embryonic form of the neural cell adhesion molecule in schizophrenic brains. PNAS 1995;92:2785–9.
[10] Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR, et al. Huntington disease Nature reviews Disease primers 2015;1:15005.
[11] Bayer R, Franke H, Ficker C, Richter M, Lessig R, Buttner A, et al. Alterations of neuronal precursor cells in stages of human adult neurogenesis in heroin addicts. Drug Alcohol Depend 2015;156:139–49.
[12] Bearden CE, Thompson PM, Dutton RA, Frey BN, Peluso MA, Nicoletti M, et al. Three-dimensional mapping of hippocampal anatomy in unmedicated and lithium-treated patients with bipolar disorder. Neuropsychopharmacology 2008;33:1229–38.
[13] Belujon P, Grace AA. Hippocampus, amygdala, and stress: interacting systems that affect susceptibility to addiction. Ann N Y Acad Sci 2011;1216:114–21.
[14] Bengochea O, Gonzalo LM. Effect of chronic alcoholism on the human hippocampus. Histol Histopathol 1990;5:349–57.
[15] Beyer JL, Kuchibhatla M, Payne ME, Moo-Young M, Cassidy F, Macfall J, et al. Hippocampal volume measurement in older adults with bipolar disorder. Am J Geriatr Psychiatry 2004;12:613–20.
[16] Bhardwaj RD, Curtis MA, Spalding KL, Buchholz BA, Fink D, Björk-Eriksson T, et al. Neocortical neurogenesis in humans is restricted to development. Proc Natl Acad Sci 2006;103:12564–8.
[17] Blumberg HP, Kaufman J, Martin A, Whiteman R, Zhang JH, Gore JC, et al. Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. Arch Gen Psychiatry 2003;60:1201–8.
[18] Blumcke I, Schewe JC, Normann S, Brustle O, Schramm J, Elger CE, et al. Increase of nestin-immunoreactive neural precursor cells in the dentate gyrus of pediatric patients with early-onset temporal lobe epilepsy. Hippocampus 2001;11:311–21.
[19] Boekhoorn K, Joels M, Lucassen PJ. Increased proliferation reflects glial and vascular-associated changes, but not neurogenesis in the presenile Alzheimer hippocampus. Neurobiol Dis 2006;24:1–14.
[20] Boldrini M, Butt TH, Santiago AN, Tamir H, Dwork AJ, Rosoklija GB, et al. Benzodiazepines and the potential trophic effect of antidepressants on dentate gyrus cells in mood disorders. Int J Neuropsychopharmacol 2014;17:1923–33.
[21] Boldrini M, Fulmore CA, Tartt AN, Simeon LR, Pavlova I, Poposka V, et al. Human hippocampal neurogenesis persists throughout aging. Cell Stem Cell 2018;22 (589–599):e585.
[22] Boldrini M, Hen R, Underwood MD, Rosoklija GB, Dwork AJ, Mann JJ, et al. Hippocampal angiogenesis and progenitor cell proliferation are increased with antidepressant use in major depression. Biol Psychiatry 2012;72:562–71.
[23] Boldrini M, Santiago AN, Hen R, Dwork AJ, Rosoklija GB, Tamir H, et al. Hippocampal granule neuron number and dentate gyrus volume in antidepressant-treated and untreated major depression. Neuropsychopharmacology 2013;38:1068–77.
[24] Boldrini M, Underwood MD, Hen R, Rosoklija GB, Dwork AJ, John Mann J, et al. Antidepressants increase neural progenitor cells in the human hippocampus. Neuropsychopharmacology 2009;34:2376–89.
[25] Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991;82:239–59.
[26] Brambilla P, Harenski K, Nicoletti M, Sassi RB, Mallinger AG, Frank E, et al. MRI investigation of temporal lobe structures in bipolar patients. J Psychiatr Res 2003;37:287–95.
[27] Brandt MD, Jessberger S, Steiner B, Kronenberg G, Reuter K, Bick-Sander A, et al. Transient calretinin expression defines early postmitotic step of neuronal differentiation in adult hippocampal neurogenesis of mice. Mol Cell Neurosci 2003;24:603–13.
[28] Briley D, Ghirardi V, Woltjer R, Renck A, Zolochevska O, Taglialatela G, et al. Preserved neurogenesis in non-demented individuals with AD neuropathology. Sci Rep 2016;6:27812.
[29] Cameron HA, Gould E. Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. Neuroscience 1994;61:203–9.
[30] Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: a meta-analysis. Am J Psychiatry 2004; 161:598–607.
[31] Cao Y, Liu P, Bian H, Jin S, Liu J, Yu N, et al. Reduced neurogenesis in human hippocampus with Alzheimer's disease. Brain Pathol 2024;34:e13225.
[32] Chen X, Huang Y, Huang L, Huang Z, Hao ZZ, Xu L, et al. A brain cell atlas integrating single-cell transcriptomes across human brain regions. Nat Med 2024;30: 2679–91.
[33] Christidi F, Karavasilis E, Rentzos M, Velonakis G, Zouvelou V, Xirou S, et al. Hippocampal pathology in amyotrophic lateral sclerosis: selective vulnerability of subfields and their associated projections. Neurobiol Aging 2019;84:178–88.
[34] Cipriani S, Ferrer I, Aronica E, Kovacs GG, Verney C, Nardelli J, et al. Hippocampal Radial glial subtypes and their neurogenic potential in human fetuses and healthy and alzheimer's disease adults. Cereb Cortex 2018;28:2458–78.

[35] Cobb JA, Simpson J, Mahajan GJ, Overholser JC, Jurjus GJ, Dieter L, et al. Hippocampal volume and total cell numbers in major depressive disorder. J Psychiatr Res 2013;47:299–306.
[36] Cole J, Costafreda SG, McGuffin P, Fu CH. Hippocampal atrophy in first episode depression: a meta-analysis of magnetic resonance imaging studies. J Affect Disord 2011;134:483–7.
[37] Cole JD, Espinueva DF, Seib DR, Ash AM, Cooke MB, Cahill SP, et al. Adult-born hippocampal neurons undergo extended development and are morphologically distinct from neonatally-born neurons. J Neurosci 2020;40:5740–56.
[38] Colle R, Dupong I, Colliot O, Deflesselle E, Hardy P, Falissard B, et al. Smaller hippocampal volumes predict lower antidepressant response/remission rates in depressed patients: a meta-analysis. World J Biol Psychiatry 2018;19:360–7.
[39] Crews L, Adame A, Patrick C, Delaney A, Pham E, Rockenstein E, et al. Increased BMP6 levels in the brains of Alzheimer's disease patients and APP transgenic mice are accompanied by impaired neurogenesis. J Neurosci 2010;30:12252–62.
[40] Czeh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, van Kampen M, et al. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. PNAS 2001;98:12796–801.
[41] Deng W, Aimone JB, Gage FH. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? Nat Rev Neurosci 2010;11:339–50.
[42] Dennis CV, Suh LS, Rodriguez ML, Kril JJ, Sutherland GT. Human adult neurogenesis across the ages: an immunohistochemical study. Neuropathol Appl Neurobiol 2016;42:621–38.
[43] Dhanabalan G, Le Maitre TW, Bogdanovic N, Alkass K, Druid H. Hippocampal granule cell loss in human chronic alcohol abusers. Neurobiol Dis 2018;120:63–75.
[44] Duman RS, Malberg J, Thome J. Neural plasticity to stress and antidepressant treatment. Biol Psychiatry 1999;46:1181–91.
[45] Duman RS, Nakagawa S, Malberg J. Regulation of adult neurogenesis by antidepressant treatment. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 2001;26:836–44.
[46] Ekonomou A, Savva GM, Brayne C, Forster G, Francis PT, Johnson M, et al. Stage-specific changes in neurogenic and glial markers in Alzheimer's disease. Biol Psychiatry 2015;77:711–9.
[47] Epp JR, Beasley CL, Galea LA. Increased hippocampal neurogenesis and p21 expression in depression: dependent on antidepressants, sex, age, and antipsychotic exposure. Neuropsychopharmacology 2013;38:2297–306.
[48] Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, et al. Neurogenesis in the adult human hippocampus. Nat Med 1998;4:1313–7.
[49] Ernst A, Alkass K, Bernard S, Salehpour M, Perl S, Tisdale J, et al. Neurogenesis in the striatum of the adult human brain. Cell 2014;156:1072–83.
[50] Falkai P, Malchow B, Wetzestein K, Nowastowski V, Bernstein HG, Steiner J, et al. Decreased oligodendrocyte and neuron number in anterior hippocampal areas and the entire hippocampus in schizophrenia: a stereological postmortem study. Schizophr Bull 2016;42(Suppl 1):S4–s12.
[51] Flor-Garcia M, Terreros-Roncal J, Moreno-Jimenez EP, Avila J, Rabano A, Llorens-Martin M. Unraveling human adult hippocampal neurogenesis. Nat Protoc 2020;15:668–93.
[52] Franjic D, Skarica M, Ma S, Arellano JI, Tebbenkamp ATN, Choi J, et al. Transcriptomic taxonomy and neurogenic trajectories of adult human, macaque, and pig hippocampal and entorhinal cells. Neuron 2022;110(452–469):e414.
[53] Galan L, Gomez-Pinedo U, Guerrero A, Garcia-Verdugo JM, Matias-Guiu J. Amyotrophic lateral sclerosis modifies progenitor neural proliferation in adult classic neurogenic brain niches. BMC Neurol 2017;17:173.
[54] García-Fuster MJ, Perez JA, Clinton SM, Watson SJ, Akil H. Impact of cocaine on adult hippocampal neurogenesis in an animal model of differential propensity to drug abuse. Eur J Neurosci 2010;31:79–89.
[55] Gomez-Nicola D, Suzzi S, Vargas-Caballero M, Fransen NL, Al-Malki H, Cebrian-Silla A, et al. Temporal dynamics of hippocampal neurogenesis in chronic neurodegeneration. Brain 2014;137:2312–28.
[56] Gomez-Pinedo U, Galan L, Matias-Guiu JA, Pytel V, Moreno T, Guerrero-Sola A, et al. Notch Signalling in the Hippocampus of patients with Motor Neuron Disease. Front Neurosci 2019;13:302.
[57] Gould E, McEwen BS, Tanapat P, Galea LA, Fuchs E. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. J Neurosci 1997;17:2492–8.
[58] Gould E, Tanapat P, McEwen BS, Flügge G, Fuchs E. Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. PNAS 1998;95:3168–71.
[59] Groisman AI, Yang SM, Schinder AF. Differential coupling of adult-born granule cells to parvalbumin and somatostatin interneurons. Cell Rep 2020;30(202–214):e204.
[60] Habib N, Avraham-Davidi I, Basu A, Burks T, Shekhar K, Hofree M, et al. Massively parallel single-nucleus RNA-seq with DroNc-seq. Nat Methods 2017;14:955–8.
[61] Hajek T, Kopecek M, Hoschl C, Alda M. Smaller hippocampal volumes in patients with bipolar disorder are masked by exposure to lithium: a meta-analysis. J psy neuroscience : JPN 2012;37:333–43.
[62] Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, et al. Amyotrophic lateral sclerosis. Nat Rev Dis Primers 2017;3:17071.
[63] Harris KL, Armstrong M, Swain R, Erzinclioglu S, Das T, Burgess N, et al. Huntington's disease patients display progressive deficits in hippocampal-dependent cognition during a task of spatial memory. Cortex; A j devoted to the study of the nervous sys behavior 2019;119:417–27.
[64] Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. Neuropsychopharmacology 2004;29:1765–81.
[65] He J, Nixon K, Shetty AK, Crews FT. Chronic alcohol exposure reduces hippocampal neurogenesis and dendritic growth of newborn neurons. Eur J Neurosci 2005;21:2711–20.
[66] Heckers S, Heinsen H, Geiger B, Beckmann H. Hippocampal neuron number in schizophrenia. a stereological study. Arch Gen Psychiatry 1991;48:1002–8.
[67] Heckers S, Rauch SL, Goff D, Savage CR, Schacter DL, Fischman AJ, et al. Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. Nature neuroscience Nature neuroscience 1998;1:318–23.
[68] Hill AS, Sahay A, Hen R. Increasing adult hippocampal neurogenesis is sufficient to reduce anxiety and depression-like behaviors. Neuropsychopharmacology 2015;40:2368–78.
[69] Hoglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, Caille I, et al. Dopamine depletion impairs precursor cell proliferation in Parkinson disease. Nat Neurosci 2004;7:726–35.
[70] Jacobs BL, van Praag H, Gage FH. Adult brain neurogenesis and psychiatry: a novel theory of depression. Mol Psychiatry 2000;5:262–9.
[71] Jin K, Peel AL, Mao XO, Xie L, Cottrell BA, Henshall DC, et al. Increased hippocampal neurogenesis in Alzheimer's disease. PNAS 2004;101:343–7.
[72] Johnson M, Ekonomou A, Hobbs C, Ballard CG, Perry RH, Perry EK. Neurogenic marker abnormalities in the hippocampus in dementia with Lewy bodies. Hippocampus 2011;21:1126–36.
[73] Kang E, Wen Z, Song H, Christian KM, Ming GL. Adult Neurogenesis and psychiatric disorders. Cold Spring Harb Perspect Biol 2016;8.
[74] Karpf J, Unichenko P, Chalmers N, Beyer F, Wittmann M-T, Schneider J, et al. Dentate gyrus astrocytes exhibit layer-specific molecular, morphological and physiological features. Nat Neurosci 2022;25:1626–38.
[75] Kee N, Teixeira CM, Wang AH, Frankland PW. Preferential incorporation of adult-generated granule cells into spatial memory networks in the dentate gyrus. Nat Neurosci 2007;10:355–62.
[76] Kempermann G, Jessberger S, Steiner B, Kronenberg G. Milestones of neuronal development in the adult hippocampus. Trends Neurosci 2004;27:447–52.
[77] Knoth R, Singec I, Ditter M, Pantazis G, Capetian P, Meyer RP, et al. Murine features of neurogenesis in the human hippocampus across the lifespan from 0 to 100 years. PLoS One 2010;5:e8809.
[78] Lazarov O, Disouky A, Sanborn M, Mostafa M, Sabitha K, Schantz A, et al. A roadmap to human hippocampal neurogenesis in adulthood, aging and AD. Research square [preprint]. 2024.

[79] Le Maitre TW, Dhanabalan G, Bogdanovic N, Alkass K, Druid H. Effects of alcohol abuse on proliferating cells, stem/progenitor cells, and immature neurons in the adult human hippocampus. Neuropsychopharmacology 2018;43:690–9.
[80] Li B, Yamamori H, Tatebayashi Y, Shafit-Zagardo B, Tanimukai H, Chen S, et al. Failure of neuronal maturation in alzheimer disease. J Neuropathol Exp Neurol 2008;67:78–84.
[81] Liu YW, Curtis MA, Gibbons HM, Mee EW, Bergin PS, Teoh HH, et al. Doublecortin expression in the normal and epileptic adult human brain. Eur J Neurosci 2008;28:2254–65.
[82] Llorens-Martin M, Jurado-Arjona J, Avila J, Hernandez F. Novel connection between newborn granule neurons and the hippocampal CA2 field. Exp Neurol 2015;263:285–92.
[83] Llorens-Martin M, Rabano A, Avila J. The Ever-changing morphology of hippocampal granule neurons in physiology and pathology. Front Neurosci 2015;9:526.
[84] Low VF, Dragunow M, Tippett LJ, Faull RL, Curtis MA. No change in progenitor cell proliferation in the hippocampus in Huntington's disease. Neuroscience 2011;199:577–88.
[85] Lu Z, Zhang M, Lee J, Sziraki A, Anderson S, Zhang Z, et al. Tracking cell-type-specific temporal dynamics in human and mouse brains. Cell 2023;186:4345–4364.e4324.
[86] Lucassen PJ, Stumpel MW, Wang Q, Aronica E. Decreased numbers of progenitor cells but no response to antidepressant drugs in the hippocampus of elderly depressed patients. Neuropharmacology 2010;58:940–9.
[87] Madsen TM, Treschow A, Bengzon J, Bolwig TG, Lindvall O, Tingström A. Increased neurogenesis in a model of electroconvulsive therapy. Biol Psychiatry 2000;47:1043–9.
[88] Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 2000;20:9104–10.
[89] Malhi GS, Mann JJ. Depression Lancet 2018;392:2299–312.
[90] Manganas LN, Zhang X, Li Y, Hazel RD, Smith SD, Wagshul ME, et al. Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain. Science 2007;318:980–5.
[91] Marder SR, Cannon TD. Schizophrenia. N Engl J Med 2019;381:1753–61.
[92] Mathews KJ, Allen KM, Boerrigter D, Ball H, Shannon Weickert C, Double KL. Evidence for reduced neurogenesis in the aging human hippocampus despite stable stem cell markers. Aging Cell 2017;16:1195–9.
[93] Mathys H, Boix CA, Akay LA, Xia Z, Davila-Velderrain J, Ng AP, et al. Single-cell multiregion dissection of Alzheimer's disease. Nature 2024;632:858–68.
[94] Mattiesen W-R-C, Tauber SC, Gerber J, Bunkowski S, Brück W, Nau R. Increased neurogenesis after hypoxic-ischemic encephalopathy in humans is age related. Acta Neuropathol 2009;117:525–34.
[95] Mertens J, Wang QW, Kim Y, Yu DX, Pham S, Yang B, et al. Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. Nature 2015;527:95–9.
[96] Moreno-Jimenez EP, Flor-Garcia M, Hernandez-Vivanco A, Terreros-Roncal J, Rodriguez-Moreno CB, Toni N, et al. GSK-3beta orchestrates the inhibitory innervation of adult-born dentate granule cells in vivo. Cell Mol Life Sci 2023;80:225.
[97] Moreno-Jimenez EP, Flor-Garcia M, Terreros-Roncal J, Rabano A, Cafini F, Pallas-Bazarra N, et al. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. Nat Med 2019;25:554–60.
[98] Nelson MD, Saykin AJ, Flashman LA, Riordan HJ. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. Arch Gen Psychiatry 1998;55:433–40.
[99] Noor H, Baqai MH, Naveed H, Naveed T, Rehman SS, Aslam MS, et al. Creutzfeldt-Jakob disease: a comprehensive review of current understanding and research. J Neurol Sci 2024;467:123293.
[100] Palmos AB, Duarte RRR, Smeeth DM, Hedges EC, Nixon DF, Thuret S, et al. Lithium treatment and human hippocampal neurogenesis. Transl Psychiatry 2021;11:555.
[101] Perry EK, Johnson M, Ekonomou A, Perry RH, Ballard C, Attems J. Neurogenic abnormalities in Alzheimer's disease differ between stages of neurogenesis and are partly related to cholinergic pathology. Neurobiol Dis 2012;47:155–62.
[102] Placido E, Koss DJ, Outeiro TF, Brocardo PS. Altered hippocampal doublecortin expression in Parkinson's disease. J Neurochem 2024;168:1514–26.
[103] Plumpe T, Ehninger D, Steiner B, Klempin F, Jessberger S, Brandt M, et al. Variability of doublecortin-associated dendrite maturation in adult hippocampal neurogenesis is independent of the regulation of precursor cell proliferation. BMC Neurosci 2006;7:77.
[104] Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, Schrag AE, Lang AE. Parkinson disease. Nat Rev Dis Primers 2017;3:17013.
[105] Ramnauth AD, Tippani M, Divecha HR, Papariello AR, Miller RA, Nelson ED, et al. Spatiotemporal analysis of gene expression in the human dentate gyrus reveals age-associated changes in cellular maturation and neuroinflammation. Cell Rep 2025;44:115300.
[106] Reif A, Fritzen S, Finger M, Strobel A, Lauer M, Schmitt A, et al. Neural stem cell proliferation is decreased in schizophrenia, but not in depression. Mol Psychiatry 2006;11:514–22.
[107] Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, et al. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature 2011;472:466–70.
[108] Sanchez-Mejias E, Navarro V, Jimenez S, Sanchez-Mico M, Sanchez-Varo R, Nunez-Diaz C, et al. Soluble phospho-tau from Alzheimer's disease hippocampus drives microglial degeneration. Acta Neuropathol 2016;132:897–916.
[109] Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 2003;301:805–9.
[110] Scott MR, McClung CA. Bipolar Disorder. Curr Opin Neurobiol 2023;83.
[111] Seki T, Hori T, Miyata H, Maehara M, Namba T. Analysis of proliferating neuronal progenitors and immature neurons in the human hippocampus surgically removed from control and epileptic patients. Sci Rep 2019;9:18194.
[112] Seri B, Garcia-Verdugo JM, Collado-Morente L, McEwen BS, Alvarez-Buylla A. Cell types, lineage, and architecture of the germinal zone in the adult dentate gyrus. J Comp Neurol 2004;478:359–78.
[113] Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. PNAS 1996;93:3908–13.
[114] Sierra A, Encinas JM, Deudero JJ, Chancey JH, Enikolopov G, Overstreet-Wadiche LS, et al. Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. Cell Stem Cell 2010;7:483–95.
[115] Sorrells SF, Paredes MF, Cebrian-Silla A, Sandoval K, Qi D, Kelley KW, et al. Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. Nature 2018;555:377–81.
[116] Spalding KL, Bergmann O, Alkass K, Bernard S, Salehpour M, Huttner HB, et al. Dynamics of hippocampal neurogenesis in adult humans. Cell 2013;153:1219–27.
[117] Stockmeier CA, Mahajan GJ, Konick LC, Overholser JC, Jurjus GJ, Meltzer HY, et al. Cellular changes in the postmortem hippocampus in major depression. Biol Psychiatry 2004;56:640–50.
[118] Stout J, Hozer F, Coste A, Mauconduit F, Djebrani-Oussedik N, Sarrazin S, et al. Accumulation of Lithium in the hippocampus of patients with bipolar disorder: a Lithium-7 magnetic resonance imaging study at 7 tesla. Biol Psychiatry 2020;88:426–33.
[119] Su Y, Zhou Y, Bennett ML, Li S, Carceles-Cordon M, Lu L, et al. A single-cell transcriptome atlas of glial diversity in the human hippocampus across the postnatal lifespan. Cell Stem Cell 2022;29(1594–1610):e1598.
[120] Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A. Anterior hippocampal volume deficits in nonamnesic, aging chronic alcoholics. Alcohol Clin Exp Res 1995;19:110–22.
[121] Sultan S, Li L, Moss J, Petrelli F, Casse F, Gebara E, et al. Synaptic integration of adult-born hippocampal neurons is locally controlled by astrocytes. Neuron 2015;88:957–72.

[122] Taffe MA, Kotzebue RW, Crean RD, Crawford EF, Edwards S, Mandyam CD. Long-lasting reduction in hippocampal neurogenesis by alcohol consumption in adolescent nonhuman primates. PNAS 2010;107:11104–9.
[123] Tan RH, Wong S, Kril JJ, Piguet O, Hornberger M, Hodges JR, et al. Beyond the temporal pole: limbic memory circuit in the semantic variant of primary progressive aphasia. Brain 2014;137:2065–76.
[124] Tartt AN, Fulmore CA, Liu Y, Rosoklija GB, Dwork AJ, Arango V, et al. Considerations for Assessing the extent of hippocampal neurogenesis in the adult and aging human brain. Cell Stem Cell 2018;23:782–3.
[125] Taylor WD, McQuoid DR, Payne ME, Zannas AS, MacFall JR, Steffens DC. Hippocampus atrophy and the longitudinal course of late-life depression. Am J Geriatr Psychiatry 2014;22:1504–12.
[126] Terreros-Roncal J, Flor-Garcia M, Moreno-Jimenez EP, Rodriguez-Moreno CB, Marquez-Valadez B, Gallardo-Caballero M, et al. Methods to study adult hippocampal neurogenesis in humans and across the phylogeny. Hippocampus 2022.
[127] Terreros-Roncal J, Moreno-Jimenez EP, Flor-Garcia M, Rodriguez-Moreno CB, Trinchero MF, Cafini F, et al. Impact of neurodegenerative diseases on human adult hippocampal neurogenesis. Science 2021;374:1106–13.
[128] Tobin MK, Musaraca K, Disouky A, Shetti A, Bheri A, Honer WG, et al. Human hippocampal neurogenesis persists in aged adults and alzheimer's disease patients. Cell Stem Cell 2019;24(974–982):e973.
[129] Tosoni G, Ayyildiz D, Bryois J, Macnair W, Fitzsimons CP, Lucassen PJ, et al. Mapping human adult hippocampal neurogenesis with single-cell transcriptomics: Reconciling controversy or fueling the debate? Neuron 2023;111(1714–1731):e1713.
[130] van Erp TG, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, et al. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol Psychiatry 2016;21:547–53.
[131] van Erp TG, Thompson PM, Kieseppa T, Bearden CE, Marino AC, Hoftman GD, et al. Hippocampal morphology in lithium and non-lithium-treated bipolar I disorder patients, non-bipolar co-twins, and control twins. Hum Brain Mapp 2012;33:501–10.
[132] Vicidomini C, Guo N, Sahay A. Communication, cross talk, and signal integration in the adult hippocampal neurogenic niche. Neuron 2020;105:220–35.
[133] Vorel SR, Liu X, Hayes RJ, Spector JA, Gardner EL. Relapse to cocaine-seeking after hippocampal theta burst stimulation. Science 2001;292:1175–8.
[134] Walton NM, Zhou Y, Kogan JH, Shin R, Webster M, Gross AK, et al. Detection of an immature dentate gyrus feature in human schizophrenia/bipolar patients. Transl Psychiatry 2012;2:e135.
[135] Wang W, Wang M, Yang M, Zeng B, Qiu W, Ma Q, et al. Transcriptome dynamics of hippocampal neurogenesis in macaques across the lifespan and aged humans. Cell Res 2022;32:729–43.
[136] Weber M, Modemann S, Schipper P, Trauer H, Franke H, Illes P, et al. Increased polysialic acid neural cell adhesion molecule expression in human hippocampus of heroin addicts. Neuroscience 2006;138:1215–23.
[137] Weber M, Scherf N, Kahl T, Braumann UD, Scheibe P, Kuska JP, et al. Quantitative analysis of astrogliosis in drug-dependent humans. Brain Res 2013;1500:72–87.
[138] Wilson 3rd DM, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM, Dewachter I. Hallmarks of neurodegenerative diseases. Cell 2023;186:693–714.
[139] Winner B, Regensburger M, Schreglmann S, Boyer L, Prots I, Rockenstein E, et al. Role of alpha-synuclein in adult neurogenesis and neuronal maturation in the dentate gyrus. J Neurosci 2012;32:16906–16.
[140] Xie XH, Xu SX, Yao L, Chen MM, Zhang H, Wang C, et al. Altered in vivo early neurogenesis traits in patients with depression: evidence from neuron-derived extracellular vesicles and electroconvulsive therapy. Brain Stimul 2024;17:19–28.
[141] Xu C, Prete M, Webb S, Jardine L, Stewart BJ, Hoo R, et al. Automatic cell-type harmonization and integration across Human Cell Atlas datasets. Cell 2023;186:5876–5891.e5820.
[142] Yamaguchi M, Suzuki T, Seki T, Namba T, Juan R, Arai H, et al. Repetitive cocaine administration decreases neurogenesis in adult rat hippocampus. Ann N Y Acad Sci 2004;1025:351–62.
[143] Yao J, Dai S, Zhu R, Tan J, Zhao Q, Yin Y, Sun J, Du X, Ge L, Xu J, et al. Deciphering molecular heterogeneity and dynamics of human hippocampal neural stem cells at different ages and injury states. eLife 2024;12.
[144] Young JK. Neurogenesis makes a crucial contribution to the neuropathology of alzheimer's disease. Journal of Alzheimer's disease reports 2020;4:365–71.
[145] Zhang ZJ, Reynolds GP. A selective decrease in the relative density of parvalbumin-immunoreactive neurons in the hippocampus in schizophrenia. Schizophr Res 2002;55:1–10.
[146] Zhao C, Teng EM, Summers Jr RG, Ming GL, Gage FH. Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. J Neurosci 2006;26:3–11.
[147] Zhou Y, Su Y, Li S, Kennedy BC, Zhang DY, Bond AM, et al. Molecular landscapes of human hippocampal immature neurons across lifespan. Nature 2022;607:527–33.
[148] Mancini V, Delavari F, Eom TY, Zakharenko SS, Schmitt E, Eliez S. How does altered function of the hippocampus contribute to the development of psychosis? Biol Psychiatry; 2025. https://doi.org/10.1016/j.biopsych.2025.06.022. Epub ahead of print. PMID: 40623620.