Review Article

Journal of General Medicine Research

# Exploiting the dialogue amongst neurogenesis as well as escalating neuro inflammationin Aging: Utilize to map lacunae, manipulating microglia along with rewire Aging: A Review

**Kulvinder Kochar Kaur*, Gautam Nand Allahbadia, Mandeep Singh**

[1](Obstt & Gynae, specialist reproductive endocrinology & Infertility specialist). Scientific Director cum Owner Dr Kulvinder Kaur Centre For Human Reproduction 721,G.T.B. Nagar, Jalandhar-144001, Punjab,India, Jalandhar-144001Punjab, India

[2](Obstt & Gynae),D.N.B Scientific Director Ex-Rotunda-A Centre for Human Reproduction 672,Kalpak Garden,Perry Cross Road, Near Otter's Club, Bandra(W)-400040 MUMBAI, INDIA

[3](Std)(Neurology) Consultant Neurologist Swami Satyanand Hospital Near Nawi Kachehri, Baradri, Ladowali road,- JALANDHAR, PUNJAB

***Correspondence Author:**
Kulvinder Kochar Kaur, (Obstt & Gynae, specialist reproductive endocrinology & Infertility specialist). Scientific Director cum Owner Dr Kulvinder Kaur Centre For Human Reproduction 721,G.T.B. Nagar, Jalandhar-144001, Punjab,India, Jalandhar-144001Punjab, India

**Received:** 15 Aug 2026, **Accepted:** 20 Aug 2026, **Published:** 24 Aug 2026

**Citation:** Kulvinder Kochar Kaur, Gautam Nand Allahbadia, Mandeep Singh. Exploiting the dialogue amongst neurogenesis as well as escalating neuro inflammationin Aging: Utilize to map lacunae, manipulating microglia along with rewire Aging: A Review. *J Gen Med Res*. 2026; 1(1), 01-36.

## Abstract

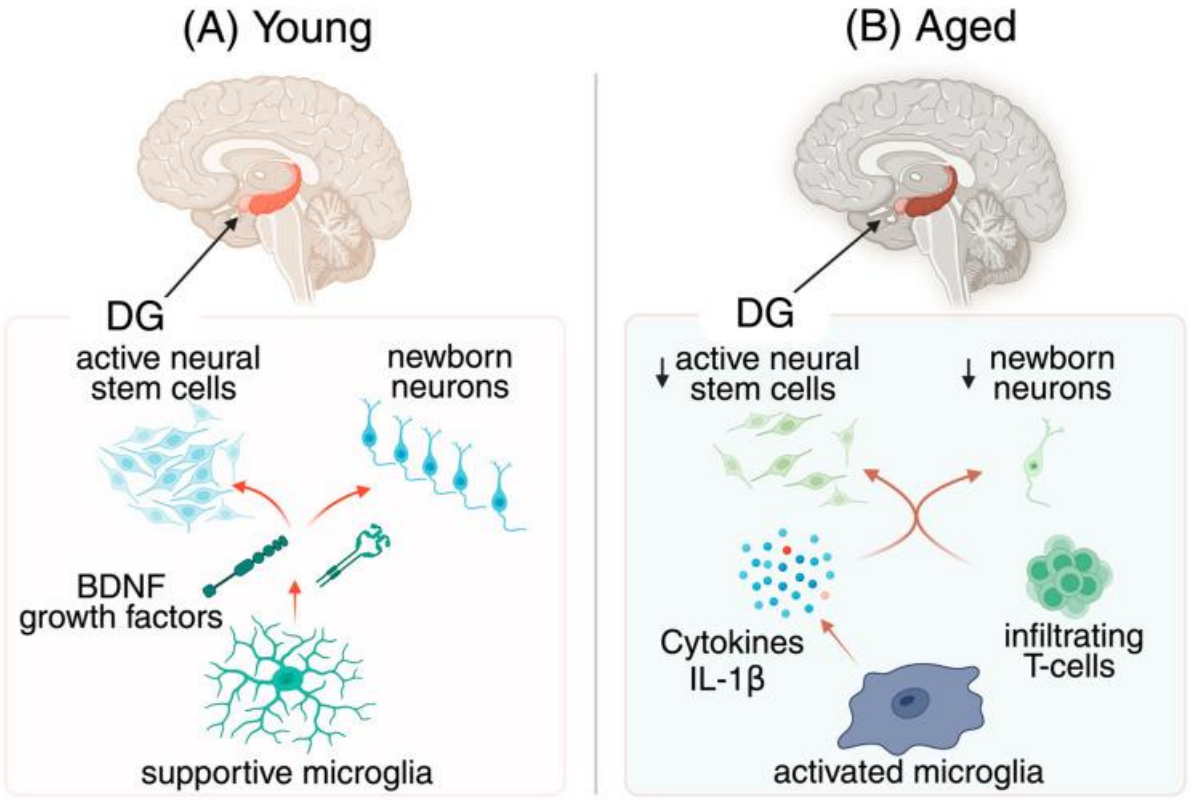
***Background:*** *Aging brains are shaped by a continuous dialogue amongst diminishing neurogenesis as well as escalating neuroinflammation. Neural stem cells propagatively possess elimination of regenerative capability, whereas microglia in addition to astrocytes switch toward maladaptive states that undermines synaptic plasticity, along with cognition. Such intersecting defines inflammaging, a gradual however unrelenting event that weaken flexibility. Nevertheless, the field continues to be hindered by pivotal lacunae: i) incomplete mapping of microglial multifaceted nature, ii) lack of insight over epigenetic scars frominflammasome signaling, iii) absence of longitudinal data, iv) unclear niche-particular immune mechanistic modes, as well as v) uncertain cross-species germaneness. This review tackles such pressing barricades, with the objective of conversion of fractionated understanding into actionable approaches. Summary: We chart the manner neurogenesis in addition to neuroinflammation operate in persistent dialogue, isolate five major information lacunae, along with explore approaches to reprogram such crosstalk. Strategies are inclusive of i) longitudinal imaging, ii) niche-focused immunomodulation, iii) glial subtype reprogramming,iv) brain-penetrant inflammasome hampering agents, as well as v) CRISPR- dependent epigenetic editing.Every approach is mapped against i) translational plausibility, ii) short-term feasibility, in addition to iii) longterm vision, with highlighting the manner mechanistic exactitude possesses the capability of driving clinical breakthrough.*

***Conclusions:*** *Here we emphasize that neurogenic plausibility is not completely eliminated however might be perpetuated or cause restoration by recalibrating immune along with epigenetic milieu. This review posits a roadmap for reshaping the aging brain's fate, yielding mechanistically grounded approaches to postpone cognitive diminishing. Further than neurology, the work butresses a wider principle: by incorporating cellular plasticity with immune modulation, science edges nearer to re-engineeringflexibility across the lifespan.*

## 1. Introduction

The brain continues to be a dynamic organ across the lifespan, persistently reshaped by the generation of new neurons in specialized niches for instance the hippocampus [1,2].Remotely from being a monument of generation, adult neurogenesis is enrichment of i) learning, ii) memory, as well as iii) emotional adaptability, iv) shielding resilience in an altering milieu [3,4]. Nevertheless, such plasticity is not limitless . With escalating age , i) neurogenic output gets exhausted, ii) cognitive reserve decreases, in addition to, iii) susceptibility to neurodegeneration escalates [5,6]. Such tension amongst a system fashioned for replenishment along with its progressive extirpation defines a central botheration for brain health, setting the stage for the manner neurogenesis as well as neuroinflammation converge in the aging brain [7,8].

Escalating age is associated with a continuous, low-grade inflammatory state usually labelled in the form of inflammaging[rev us ], an event unique from acute infection however possesses equivalent impact in shaping brain health [9,10]. In such slow-burn event unfolding over years to decades, microglia progressively have elimination of their homeostatic harmony , supporting pro-inflammatory phenotypes which liberate cytokines in addition to chemokines [11,12,revin 13] (Figure 1).




Legend for Figure 1.

Courtesy ref no-13- Neurogenesis–neuroinflammation dynamics across the lifespan. (A) Young: In the healthy young dentate gyrus (DG), enriched as well as actively cycling neural stem cells form newborn neurons which successfully mature in addition to incorporate into local circuits. Embracive microglia sustain s a trophic milieu by liberating BDNF , along with other growth factors, that facilitate stem-cell activation as well as neuronal differentiation Arrows indicate pro-neurogenic signaling from microglia to stem cells and forward progression from stem cells to newborn neurons. (B) Aged: In the aged DG, stem-cell activation declines and fewer newborn neurons are produced. Microglia adopt reactive phenotypes in response to extrinsic cues (DAMPs, cytokines, peripheral immune signals, metabolic stress, BBB leakage) and intrinsic programs (epigenetic priming/innate immune memory, mitochondrial impairment, senescence-linked remodeling), along with liberate pro-inflammatory cytokines for instance IL-1β which reppress neurogenesis Arrows highlight the switching from embracive trophic signals to inflammatory hints along with the resulting diminished neuronal output. BDNF, brain-derived neurotrophic factor; DG, dentate gyrus; IL-1β, interleukin-1 beta. Created in Biorender. Tanaka, M. (2026) https://BioRender.com/pjz1qcu.

Astrocytes augment such tone, switching toward reactive states which erode trophic embracing as well as disturb neuronal networks [14,15]. Vascular changes escalateinimicality of the blood–brain barrier (BBB), whereas peripheral immune signals infiltrate in addition to butress local inflammation [16,17]. Collectively , such subtle however continuous disturbance accrual takeplace across 30-40years, propagatively changing cellular behavior, along with circuit . flexibility [18–20].

Across the aging hippocampus, two interwoven directions materialize: a constant reduction in neurogenesis as well as a propagative escalation in neuroinflammation [21,22] (Figure 1). Reduced neural stem cell activity in addition to dysfunctional maturation of adult-born neurons reduce pattern separation, resilience in memory approaches, along with mood controlling [23,24]. Simultaneously, microglia switching takes place toward a proinflammatory state, liberating cytokines for instance interleukin-1 beta (IL-1β) as well as TNF whereas yielding diminished trophic embracing , thus changing the niche [23,25].

Instead of different occurrence , these arcs intersect into a bidirectional dialogue in which inflammation restricts neurogenesis, in addition to neurogenic failure augments susceptibility to inflammatory stressors [8,26].

Microglia work in the form of finely tuned gatekeepers of the neurogenic niche, shaping if new neurons flourish or fail [27,32] (Figure 1). In youthful circumstances, they remove apoptotic cells, carve synapses with precision, as well as liberate trophic factors for instance brain-derived neurotrophicfactor (BDNF) in addition to IGF-1 which maintain progenitor proliferation, along with survival [27,33].

(Figure 1A). Nevertheless, i) chronic inflammatory tone rewires their working: ii) cytokine liberationexacerbates, iii) complement-guided pruning accelerates, as well as iv) phagocytic activity assumes prejudice toward depleting viable cells [34,35]. Such switching represses neurogenesis, interferes with circuit incorporation, in addition to cherishes susceptibility [32,36]. Pivotally, youthful microglia are not simply less reactive; they are actively programmed toward pro-neurogenic states that are propagatively eliminated with age [34,37].

Empirical models illustrate that inflammatory injuries strikingly restrain adult hippocampal neurogenesis [38,39]. i) Acute lipopolysaccharide challenges, ii) chronic peripheral inflammation, or iii) autoimmune damages diminish i) progenitor proliferation, ii) neuronal survival,along with iii) incorporation [40,41]. On the other hand, targeted arbitrations varying from i) pharmacological agents to ii) trophic factors rescue facet of neurogenesis by blunting microglial activation or rectification of signaling cascades for instance i) PI3K-Akt, ii) ERK, iii) or wingless-related integration site signaling pathway (Wnt)/β-catenin [42,43]. Nevertheless, validation points to take precautions against simple “antiinflammation” strategies: i) both escalated repression as well as continued activation possesses the capability of being inimical [36,44]. Results are based on i) timing, ii) magnitude, in addition to iii) niche circumstances, iv) buttressing the requirement for mechanistic preciseness in modulating pathways, v) microglial states, along with v) local milieus [8,45].

Although escalating corroboration, plethora of lacunae dampen interpretation in the form of etiological factor as well as curtails translation.

Gap 1 delineate ‘s the paucity of longitudinal, amongst subject outcomes which track the manner co-evolution of niche inflammation in addition to neurogenesis takes place over aging, stress exposure, as well as rectification [46,47].
Gap 2· portrays that microglial in addition to astrocytic multifaceted nature is substantial however occasionaly mapped at neurogenic zones with adequate spatial , along with temporal resolutiontill now [48,49].

Gap 3 mirror’s that inflammasome-associated innate immune memory might stabilize antineurogenic programs, however cell- kind–particular continuation as well as reversibility continues to be uncharted [50,51].

Gap 4 delineate ‘s that i) vascular, ii) BBB, in addition to iii) peripheral immune accounting for are usually treated in the form of background variables instead of estimated guides [52,53].

Gap 5 portrays that cross-species coordination continues to be underpowered, complicating interptretation about which mechanistic modes are shared vis a vis model-bound [54,55].

This review sets out a playbook for rewiring the neuroimmune dialogue by associating deeper understanding of mechanistic modes to translationalapproach. We map unresolved lacunae to actionable strategies: i) longitudinal neuroimmune imaging to catch temporal etiologicalfactor, ii) niche-concentrated immunomodulation in reference to tune local signals, in addition to iii) glial sub kinds reprogramming in reference to rectification of embracive states or iv) form new neurons as well. v) a) We emphasize brain-penetrant nucleotide-binding domain, leucine-rich-repeat containing family, pyrin domain-containing (NLRP3) inflammasome hampering agents along with b) nucleic acid therapeutics in the form of near-term approaches c) regarding breaking maladaptive IL-1β loops, d) whereas CRISPR-based epigenetic editing delineates a longer-horizon gadget to reset maladaptive chromatin programs. e)Collectively, such advancements reframe therapeutic feasibility in aging.
i) Perpetuating a youthful neurogenic niche is attractive ii) of maintaining cognitive reserve, resulting in iii postponement of neurodegeneration, as well as iv) escalating flexibility across the lifespan [56].

Mechanistic advancements display that both lifestyle factors as well as molecular mediations possesses the capability of i) counter inflammaging, ii) rejuvenate progenitors, in addition to iii) leads to restoration of plasticity [57]. The botheration is switching from associations to actionable approaches whichcoordinate biology with translation [58].

This review charts that direction by i)first detailing the interlaced biology of neurogenesis, along with neuroinflammation, ii) followed by interrogating five pivotal lacunae that obscure causality, as well as iii) Lastly, evaluationof appearing strategies with human applicability in view, guiding readers from concept to clinic-ready postulated.

Earlier we had reviewed part of SIRTs in the form of epigenetic modifiers regarding postponement of Diabetic Kidney Disease(DKD)& in placental growth in pregnancy besides , part of NLRP3 Inflammasome, in Reproduction. Additionally, we reviewed the pivotal part of oxidative stress( OS) in the generation of neurodegenerative diseases(NDD) for instance Amyotrophic Lateral Sclerosis (ALS), Alzheimer's Disease (AD), Parkinson's disease (PD), part of Gut Microbiota dysbiosis in NDD generation as well as ischaemic Stroke development ,Role of Bile Acids in NDD generation inclusive of ALS, AD ,PD , HD in addition to priondisease. Furthermore, how adenylyl cyclases (ACs) might be the therapeutic targets regarding neurodegenerative diseases(NDD) ,role of Mitochondrial Melatonergic Pathwayin generation of type 1 diabetes mellitus,& PD , &the manner dysfunctional glymphatic system is held responsible for the generation of NDD & by buttressing NAD+ for tackling ovarian ageing related to infertility for tackling ovarian ageing related to infertility and on the part ofhow immunosenescence and inflammageing participate in escalating generation of viral and bacterial diseases or pathological ageing with poor response to challenges as confrontedduring the COVID pandemic & late onset male hypogonadism [59-73].

Here In this review, utilization of word microglia ismade basically regarding microglia that are yolk sac– obtained parenchymal microglia positioned amongst the brain parenchyma. Nevertheless, plethora of studies we detail depend on broad myeloid markers for instance Iba1 or CD11b, that do not entirely differentiate parenchymal microglia from other tissue-resident brain macrophages inclusive of i) perivascular, ii) meningeal, as well as iii) choroid plexus macrophages or from iv) infiltrating monocyte- obtained macrophages. Where the original data do not clearly differentiate such populations, we hence utilize term v) microglia/macrophages in addition to interpret the documented actions on neural stem, along with progenitor cells (NSPCs) as stemming from mixed myeloid subsets instead of microglia alone. Compared to that, when microglia are selectively targeted by i) genetic, ii) pharmacological, iii) or elimination approaches, we explicitly assigned the found pro- or anti-neurogenic actions on NSPCs to parenchymal microglia. Etiological interpretation should be restricted to studies that utilize microglia-selective disturbances; otherwise, the inference of observations are better done in the form of mirroring niche-level inflammatory impacts.

## 2. Neurogenesis along with Neuroinflammation in the Aging Brain: An Overview

Adult mammalian brains hold on to a restricted capability for neurogenesis, restricted primarily to the dentate gyrus (DG) of the hippocampus as well as the SVZ zone, where neural stem cells in addition to NSPCs form new neurons which incorporate into existing circuits [74,75]. Compared to that, in the neonatal brain NSPCs are organized apart from amongst such classical neurogenic zones however further across extra areas for instance the i) cerebral cortex,along with ii) such neonatal progenitors display a)molecular as well asb )working traits which vary from adult NSPCs[76]. Corresponding to microglia NSPCs are not a uniform pool but embody unique subkinds with i) variable extents of quiescence, ii) proliferative capability, in addition to iii) lineage prejudice, iv) specifically possesses the properties of well studied in the SVZ, where type B, C,along with A cells have been displayed in both neonatal as well as adult brains [77,78]. v) Such event declines with age, as stem cells embrace a primed, pro-inflammatory phenotype, liberating cytokines for instance i) IL-1β in addition to ii) TNFα which result in a) dysfunctional progenitor proliferation , along with b) neuronal differentiation [79,80]. By contrast, anti-inflammatory in addition to trophic factors for instance i) IL-4, ii) IL-10, iii) IGF-1, as well as iv) BDNF facilitated neurogenesis [81,82]. The orchestration amongst such converse signals switches at the time of "inflammaging," when systemic immune mediators along with infiltrating cells escalatingly shape the neurogenic niche [79,83–85].

### 2.1. Adult Neurogenesis: Mechanistic Modes along with Age- Associated Reduction

Adult neurogenesis in the mammalian brain takes place basically in two distinct areas, i) the subgranular zone of the hippocampus as well as the ii) SVZ zone of the forebrain, where neural stem cells maintain lifelong plasticity by producing new neurons in addition to glia [86,87]. Amongst such niches, stem cells undergo consecutive steps of i) proliferation, ii) lineage commitment, as well as iii) differentiation into a) intermediate progenitors b) that eventually mature into working granule neurons or glial cells [88,89]. Newly produced neurons propagate via i) migration, ii) synaptic incorporation, in addition to, iii) circuit integration, hence reshaping a) hippocampal along with b) olfactory networks c) whereas sustaining a dynamic harmony amongst neuronal, along with glial lineages [90,91].

The controlling of adult neurogenesis delineates a delicate interaction amongst intrinsic genetic programs as well as extrinsic milieu tips [78,92]. Transcription factors in addition to epigenetic mechanistic modes orchestrate lineage propagation, driving neural stem cells from quiescence toward neuronal or glial differentiation [74,93]. Concomitantly , the neurogenic niche yields trophic embracing , vascular inputs, glial signaling, along with

neuronal actions that maintains proliferation as well as incorporation [94,95]. Working , in the form of a dynamic aiding in coordinator, the niche incorporates such signals to perpetuate stem cell working in addition to guarantee neurogenesis outputin harmony under physiological situations [96,97]. Rodent studies constantly illustrated that adult neurogenesis undergoes a steep reductionswith advancing age, pointed by decline reduced progenitor proliferation and a shrinking contribution of new neurons to hippocampal circuits [98,99]. Whereas neural stem cells are preserved, their output is restricted by i) continued quiescence, ii) asymmetric division, as well as iii) intrinsic changes for instance decreased lamin B1 expression [100,101]. Aging possesses equivalent meaningful micromilieu: i) diminished trophic embracing, ii) vascular impairment, in addition to iii) escalated TGF- β , along with iv) inflammatory signaling restrain neurogenic probability [102,103]Such observations buttress that the diminishing is not owing to progenitor elimination however to niche inimicality, that curtails activation as well as differentiation although possesspreserved stem cell reservoirs [104-106].
Mounting corroboration from human postmortem as well as imaging studies pointed that hippocampal neurogenesisplausibly gets retained across adulthood, with several asssessments estimating thousands of immature neurons in healthy persons with as high as 70's to 80's yrs [1, 107]. However, other studies detail steep age- associated reductions in proliferation in addition to neurogenic markers, although the persistent presence of progenitor cells [23, 108]. Such debatable observations are usually assigned to methodological variations in tissue processing, along with marker estimation [109, 110]. Thedilemma that results contrasts with rodent data, where neurogenic plausibility persists however niche decrease dominates, generating a translational uncertainty that frames ongoing cross-species contrastings [107,111].

### 2.2. Neuroinflammation in Aging: Microglia along with Further than Them

The aging brain possesses the properties of having a propagativeremodeling of its immune panorama , where a state of low-grade however chronic neuroinflammation becomes a defining benchmark [112–114].

Central to such switching are microglia, the resident immune cells that i) propagatively eliminate their homeostatic as well as ii) reparative working iii) whereas embracing pro-inflammatory, neurotoxic phenotypes[11,12, 115]. Benchmarks of aged microglia are inclusive of i) changed transcriptomes, ii) dystrophic morphology, iii) dysfunctional phagocytosis, in addition to iv) exacerbated cytokine liberation [11,116,117]. Nevertheless, microglia do not work alone; i) astrocytic immunosenescence, along with ii) peripheral immune inputs further augment inflammatory tone, compared sharply with the embracing milieu of younger brains [118-120]. Astrocytes are not passive onlookers: with age they enter reactive programs (usually detailed in the form of A1/A2-like, however better perspective is in the form of a gamut of reactive states) that reshape synaptic as well as stem-cell niches [14, 121,122]. Reactive astrocytes liberate cytokines/chemokines in addition to gliotransmitters (for instance ATP, glutamate, D-serine) that possess the capability of i) augmenting inflammatory signaling , along with ii) directly prejudice neural stem/progenitor cella) quiescence,b)proliferation, as well as c)lineage decisions [27, 123, 124].Via their endfeet at the blood brain barrier(BBB), astrocytes work in the form of gatekeepers of barrier permeability in addition to immune-cell entry, whereas their metabolic coupling (lactate shuttling, lipid/cholesterol handling) possesses the capability of either buffer or fuel neuroinflammatory tone [123-125]. Microglia astrocytes signals (for instance IL-1– associated as well as complement- associated hints ) facilitate astrocytic reactivity, whereas astrocyte-to-microglia signals possess the capacity of interchangeably recalibrating microglial state, generating a local augmentation loop [123, 126, 127]. In neurogenic areas, such astrocyte–microglia axis working is in the form of a signal amplifier in addition to gatekeeper which aids in estimating if inflammatory episodes cause rectification with resolution of neurogenesis or consolidate into a chronically hampering niche [27, 123, 128].

Aged microglia are portrayed by i) dystrophic morphology, ii) diminished phagocytic capability ,along with iii) transcriptional reprogramming iv) which promotes pro-inflammatory gene expression over reparative working [11,130,131]. Such inimicality is exacerbated by microglial priming, an event in which earlier immune or metabolic botherations leave cells in a state of innate immune memory, potentiating their reactiveness to following injuries [131–133].

Primed microglia liberate exacerbated quantities of cytokines for instance IL-1β, IL-6, along with TNFα, causes dysfunctional synaptic plasticity as well as aggravating neurodegeneration [18, 132, 134]. Despite , once replaced empirically, aged microglia possess persistence of their hyperreactivity owing to niche- guided tips, buttressing the manner priming locks prejudice the aging brain into a maladaptive inflammatory state [130,135]. A vital open query is timing: when do inflammatory in addition to metabolic hits switch the niche from adaptive plasticity to continuous antineurogenic prejudice? . Further than such structural as well as transcriptional switches, chronic activation of inflammatory pathways— inclusive of NF-κB signaling in addition to, NLRP3 inflammasome activity—incepts in the form of a central guide of aging-linked microglial impairment [136,137]. Their continuous activation maintains the liberation of i) IL-1β, ii) IL-6, along with iii) TNFα, a) generating an antagonistic milieu b) that generates attrition of neuronal survival in addition to, c) is associated to diminishing adult neurogenesis in inflammatory along with aging models [138–140]. Such cytokines i) cause dysfunctional progenitor proliferation, ii) prejudice glial differentiation, as well as iii) disturb synaptic plasticity, propagatively switching the neurogenic niche from embracive to hampering [8, 141, 142]. Meaningfully, mitochondrial impairment as well as oxidative stress(OS)

cycle of chronic inflammation which erodes regenerative capability in the aging brain [140,143–146].

With advancing age, the BBB becomes escalatingly permeable, imposes inimicality on its selective working, along with allowing infiltration of peripheral immune cells [17, 147]. Of these, accrual of CD8+ T cells takes place in neurogenic niches of i) aged mice as well as ii) humans, where they liberate a) interferon-γ in addition to b) other cytokines which reppress i) neural stem cell proliferation , along with ii) neuronal differentiation [148,149]. Aged microglia further facilitate such event by liberating chemokines as well as remodeling the niche micromilieu, generating a feed-forward inflammatory loop [52,150]. In sharp contrast, the young brain maintains a largely anti-inflammatory, pro-neurogenic environment , emphasizing the manner immune remodeling with age shifts the orchestration away from regeneration toward chronic impairment [35, 150,151]

### 2.3. Microglia–Neural Stem Cell Interaction

Microglia have incepted in the form of i) central organizers of adult neurogenesis, ii) engaging in a persistent dialogue with a) neural stem in addition to b) progenitor cells which shapes each stage of the event [33, 152, 153]. iii) Poles apart from passive sentries, iv) they actively carve the neurogenic niche by a) phagocytosing apoptotic newborn cells, iv) hence sustaining homeostasis as well as v) estimating which neurons survive to maturity [153,154]. Microglia further result v)in improvement of synaptic connections of adult-born neurons through a) selective trimming , b) guaranteeing appropriate incorporation into circuits already present [32,33, 155]. v) Further than such structural parts, a) their secretome exerts robust impacts , b) liberating circumstance based tips which either i) facilitate proliferation in addition to ii) differentiation or iii) curtail neurogenesis, iv) emphasizing their double capability in the form of nurturers or hampering agents [153, 156].

In the young brain, microglia commonly embrace phenotypes which nurture instead of hamper neurogenesis [157–159]. By liberating trophic factors for instance BDNF, IGF-1, and TGF-β, they stimulate neural stem cell proliferation, drive differentiation, along with facilitate survival of newborn neurons [27, 159,160]. Abundant milieu as well as physical actions further escalate this embracive role, switching microglia toward anti-inflammatory states which augment plasticity in addition to circuit incorporation [27, 161,162]. M2-polarized microglia specifically cultivate neuronal differentiation, along with synaptic maturation, buttressing their capability of translating systemic as well as local signals into pro-neurogenic results [163–165]. Such trophic partnership emphasises microglia vital in the form of comrades in perpetuating hippocampal flexibility early in life [27,28,158 ] .

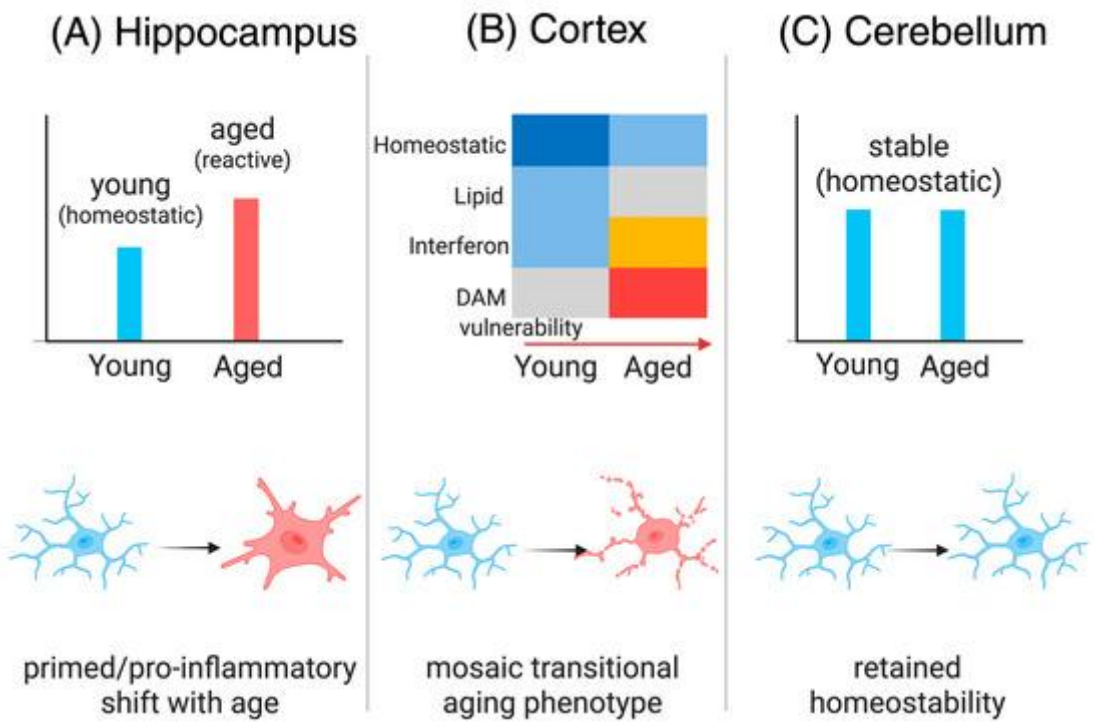
Aging as well as chronic stress earnestly interfere with microglia–neural stem cell crosstalks, in addition to are correlated with switches toward pro-inflammatory, damage- reactive microglial programs which possess the capacity of becoming neurotoxicity- associated particular circumstances [30,131]. In this maladaptive phenotype, microglia liberate escalate quantities of IL-1β, TNFα,along with IL-6, which suppress NSC proliferation, diminished BDNF accessiblity , as well as block the maturation of newborn neurons [12,31,115]. Simultaneously , microglia eliminate their phagocytic harmony , resulting in aggravated or abnormal clipping which compromises neuronal survival as well as, synaptic plasticity [11, 115,166]. Dysfunctional autophagy in addition to metabolic impairment aggravate such alterations, in addition to microglial priming—together with BBB changes along with peripheral immune inputs— possesses the capability of stabilizing inflammatory niche states that propagatively jeopardizes regenerativeplausibility. Microglia–NSC crosstalk is mediated by i) finely tuned molecular pathways, with the ii) C-X3-C motif chemokine ligand 1 (CX3CL1)–C-X3-C motif chemokine receptor 1 (CX3CR1)axis iii) incepting in the form of a central governer of microglial activation, iv) synaptic incorporation , as well as iv) neurogenic embracing [29,168]. Such signaling i) sustains microglial quiescence, ii) curtails cytokine liberation , in addition to iii) promotes appropriate maturation of adult-born neurons, iv) whereas its interference with result in a)dysfunctional dendritic spine generation , along with b)neurogenesis [168–170]. Other modulators, inclusive of i) cytokines, ii) chemokines, as well as iii) extracellular vesicles (EVs), complement this dialogue byshaping microglial states as well as their impact on progenitors [171–173]. With aging, i) switching of such pathways from protective to maladaptive, ii) cherishing chronic inflammation in addition to iii) reduced neurogenic output, iv) thereby emphasizing their therapeutic germaneness , v) which cites basically the validation behind every pathway [29,174].

## 3. Vital Lacunae in Current Knowledge

Building on the five lacunae launched above, the following sections coordinate mechanistic uncertainties with practical empirical in addition to translational strategies

### 3.1. Lacuna 1—Area-ParticularMicroglial Variability in Aging

Microglia are escalatingly acknowledged in the form of a multifaceted population whose identities differ across brain areas instead of fitting a uniform template [48]. Transcriptomic as well as single-cell profiling studies display unique gene expression in addition to morphological characteristics in microglia from the i) cortex, ii) hippocampus, iii) cerebellum, iv) along with other areas, with i) certain subsets tuned toward surveillance as well as ii) others toward immune activation [175]. Such area- in addition to cell-kind associations are summarized in Figure 2. Aging augments such variations, reshaping transcriptional signatures in an area - based fashion , along with accentuating selective susceptibilities [48]. Such variations delineates a vital however underexplored influencer of brain aging as well as adaptability [113].




**Legend for Figure 2.**

**Courtesy ref no-13-** Region-specific microglial diversity and aging. (A) Hippocampus: Hippocampal microglia switch from a pronouncedly homeostatic profile in young animals to a primed, pro-inflammatory state with aging. This is illustrated by escalated reactive microglial signatures as well as escalated inflammatory markers, delineating thepotentiated susceptibility of the neurogenic dentate gyrus (DG). The upward arrow indicates an age- associated escalation in priming in addition to, inflammatory activation (B) Cortex: Cortical microgliaillustrate a mosaic, transitional aging phenotype. The heatmap summarizes relative transcriptional actions activities—homeostatic, lipid- correlated , interferon-responsive along with DAM (disease-associated microglia) susceptibility—across young as well as aged states. Color gradients and the horizontal age-arrow illustrate the manner such signatures switch multifaceted nature with age, emphasizing plethora of partially overlapping microglial subtypes instead of a uniform transition Dark blue—high homeostatic action; Light blue—moderate homeostatic action; Grey—lipid- correlated action; Yellow—interferon-responsive action ; Red—high DAM- susceptibility action (C) Cerebellum: Cerebellar microglia largelyperpetuate a stable, homeostatic phenotype across aging. Bar plots and conceptual illustrations illustrateminimal alteration in activation markers, in addition to microglia continues to be pronouncedly ramified with curtailed switch toward inflammatory states Overall interpretation: Microglial aging is regionally variable . Hippocampal microglia tend toward primed, pro-inflammatory profiles; cortical microglia embrace mixed , along with transitional states; as well as cerebellar microglia sustain homeostability. This multifaceted nature displays that aging does not uniformly reprogram microglia across the brain in addition to buttresses the requirement for spatially customized therapeutic approaches targeting area -specific susceptibilities. DAM, disease-associated microglia

Aging imprints unique signatures on microglia across brain areas , displaying sharp comparison to phenotype along with working [48]. In the hippocampus, transcriptomic assessment show upregulation of adhesion as well as motility genes, coordinating with greater sensitivity to inflammatory in addition to metabolic stress, while cerebellar microglia apparently are relatively stable[48] (Figure 2A). Eempirical botherations further buttress such diversity: TNFα or systemic LPS evoke powerful , along with continued activation in hippocampal microglia, yet only blunted reactions in other areas [176]. Such observations emphasise that microglial aging is not uniform [48]. What continues to be uncharted is the manner such area -particular switches i) shape neuronal survival, ii) plasticity, as well as iii) eventually cognitive aging [113]. Neurogenic areas for instance the DG as well as SVZ zone depend on intricate crosstalks amongst neural stem cells in addition to local microglia, however if such microglia reveals distinct aging trajectories continues to be uncharted question [22] (Figure 3C). Corroboration points that niche-resident microglia possess skilled parts, from embracing neuroblast migration to manipulating survival signals [177]. With age, however, such populations undergo positional remodeling as well as propagative activation which might generate antineurogenic milieu [150].

What is lacking is systematic mapping of their transcriptional in addition to working states across the lifespan [21]. Without such resolution, it is tough to extricate if neurogenesis diminishes basically from local niche inimicality or delineates

wider systemic switches in microglial aging [178].

Rectification of the manner microglial disparity shapes neurogenic decline carries earnestrepercussions for therapy [179]. If hippocampal microglia are specifically susceptible to embracing pro-inflammatory, anti-neurogenic profiles with aging, whereas SVZ microglia perpetuate greater embracive working , this possesses the capability of aiding in expositions of selective susceptibilities in cognition as well as neurodegeneration [180]. These uniqueness point that arbitrations are not needed to quieten microglia globally however rather target maladaptive phenotypes in particular areas [49].

High-resolution profiling of microglial states in neurogenic versus non-neurogenic areas would hence be vital [181]. Such understanding possess the capacity of helping customized approaches which aids in rectification of hippocampal neurogenesis locally whereas perpetuating advantageous immune surveillance in other areas [182].

### 3.2. Lacuna 2—Inflammasome- Driven Epigenetic Alterations

Continuous activation of the NLRP3 inflammasome has materialized in the form of a benchmark of brain aging, shaping a chronic inflammatory milieu which disrupts neuronal as well as stem cell homeostasis [183]. Apart from acute reactions , that are transitory in addition to confer protection , aged microglia continue to be locked in an overactivated state, guiding persistent liberation of IL-1β, along with interleukin-18 (IL-18) [184]. Sustenance of such output fuels neuroinflammation, accentuates synaptic impairment, as well as exacerbates neuronal elimination [183]. Corroboration from Alzheimer's disease (AD) in addition to other age- associated circumstances illustrates that NLRP3 activation is i) sustained by metabolic stressors, along with ii) amyloid accrual , iii) displaying it in the form of a central stimulator of the pro-inflammatory niche property of the aged brain [185].

iv) A mounting corroboration illustrates that aged microglia possess persistent an epigenetic memory of prior inflammatory happenings, with persistent "scars" left behind maintaining maladaptive activity [186]. Hypomethylation of the IL-1β promoter, for example, sustain exaggerated cytokine liberation in aging brains and guides continuous neuroinflammation [186]. Such chromatin- dependent reprogramming distinguishes transitory immune reactions from longlasting impairment [186]. Neural stem cells in inflamed niches might go through analogous repressive modifications at pro-neurogenic loci, declining their regenerative plausibility [187].

Corresponding, with hematopoietic stem cells, where chronic inflammasome signaling reshapes enhancer availability, buttressing the manner inflammation imprints itself epigenetically to restraint stem cell working across tissues [188].

If inflammasome signaling directly reshapes the epigenome of neural stem cells in the DG or SVZ zone continues to be an uncharted query [189]. NSCs in such sites might attain repressive chromatin marks which dampen their regenerative reactions substantially subsequent to inflammatory hints subside , however systematic corroboration is missing [189]. Does inheritance of such 'epigenetic scars,' takes place in aged NSCs,thus stabilizing diminished neurogenic plausibility ? Whether so, such marks might diminish the ceiling of healing despite subsequent to inflammatory cues ebb , that enables full rejuvenation difficult without targeted resetting [189]. Present studiesdetail epigenetic controlling in adult NSCs as well as chromatin remodeling at the time of aging, however they occasionaly investigate inflammasome-guided mechanistic modes [93]. Without detailed chromatin in addition to transcriptomic maps of inflamed niches, the association amongst continuous inflammation , along with neurogenic failure continues to be conjectural [189].

If inflammasome activity imprints persistentcontinuation of epigenetic scars on neural stem cells, such alterations possess the capacity of continuously blunting neurogenesis as well as diminishing the ceiling of regenerative reactions , despite subsequent to dissipation of inflammatory hints [190,191]. Nevertheless, studies of ischemia in addition to stroke in rodents , along with humans illustrate that locally activated, injury-reactive stem cells with reprogrammed phenotypes even possess the capacity of getting recruitment amongst sites with injuries as well as assist in neurogenesis [192,193]. Thus, instead of an absolutely "locked" state, inflammasome-guided epigenetic memory might switch neural stem cells along a spectrum of diminished however even now possessing reactivatable plausibility , with meaningful repercussions for the manner we fashion mediations in reference to resetting the niche.

### 3.3. Lacuna 3—Longitudinal Dynamics of Neuroimmune Interactions

Maximum studies evaluating the give-and-take amongst neuroinflammation in addition to neurogenesis depend on static snapshots, canonically comparing young, along with old animals or estimating endpoints subsequent to an inflammatory damage [194]. Whereas these fashions capture wide variations,they do not possess the capacity of rebuilding dynamic directions or display etiological order [195]. It continues to be uncharted whether inflammatory alterations take place prior to neurogenic reduction, stemming analogously , or take place subsequent to in the form of a secondary sequelae [194]. Augmentation of our insight have been obtained through cross-sectional single-cell as well as epigenomic studies of cell states, however they just yield frozen moments in time,thus omitting the temporal choreography of neuroimmune aging uncharted [196].

The manner detailed in Section 2.2, a core uncharted avenue is timing—when inflammatory in addition to metabolic disturbances transit from adaptive reactions to

continuous antineurogenic prejudice . Tackling this needs amongst -subject, longitudinal strategies which possess the capacity of resolution of sequence , along with etiological factor instead of depending on cross-sectional snapshots( alias a quick summary or visual representation of a specific moment in time).

Abridging the temporal gap would need advancements in techniques that switches further than static estimates [197]. Longitudinal in vivo imaging of both neurogenesis as well as neuroinflammation, associated with surfacing PET tracers, provides one favourable path [198]. Corresponding generation of peripheral as well as central biomarkers, beside chronic empirical archetypal instead of acute LPS concerns, possesses equivalent vitality [199]. Eventually , incorporated approaches which associate molecular, cellular, in addition to systems-level dynamics are the requirement to catch the manner neuroimmune interactions unfold across the lifespan [200].

Clarification of the temporal sequence amongst inflammation in addition to, neurogenesis is vital for getting insight into brain aging [22]. If chronic inflammation confirms to be a guide, sequelae , or both in neurogenic decline, this would foundationally reshape approaches for perpetuating neural plasticity [201]. Untangling such interactions is thus imperative for precision strategies which shield neurogenic capability over the lifespan as well as eventually inform the manner we fashion treatments regarding sustenance of cognition in addition to flexibility in aging [202].

3.4. Lacuna 4—Niche-Particular Immune Mechanistic Modes
The subgranular zone (SGZ) of the hippocampus as well as the SVZ of the lateral ventricles generate substantially skilled neurogenic niches, unique from the wider brain parenchyma [95]. Such micromilieu bring together i) neural stem cells, ii) progenitors, iii) astrocytes, iv) microglia, v) endothelial cells, in addition to, in aging, vi) infiltrating immune cells as well [95]. However, although advances in transcriptomic , along with proteomic profiling, even now we have absence of an appropriate map of which immune as well as inflammatory signals amongst such niches directly control stem cell activity [203]. Equivalently uncharted is if resident or infiltrating immune cells are predominant inrepressing neurogenesis at the time of aging [203].

Mounting corroboration involves inflammatory hints in the form of main hampering agents of neurogenesis amongst the SVZ as well as subgranular zones [203]. Microglial-obtained cytokines for instance i) IL-1β, ii) TNFα, in addition to iii) IL-6 constantly materialize in the form of candidates, whereas monocyte infiltration, along with CD8+ T cell activity in the SVZ have further been associated with reduction of neurogenic plausibility [148]. However, etiologicalfactor as well as germane contributions continues to be uncharted [204]. Additionally systemic inflammation further makes matters worse by changing BBB wholeness in addition to selectively reshaping niche immune constitution , however the permeability , along with susceptibility of such regions continues to be badly defined [205].

Partial of such uncertainty delineates drawbacks of the present in vivo gadget kit for dissecting NSPC–microglia/ macrophage interactions. There are still no broadly supported strategies which repress either NSPCs or microglia/ macrophages in a totally selective as well as temporally exact fashion in the intact brain. Pharmacological in addition to toxic archetypal for instance CSF1R hampering agents or liposomal clodronate are capable of eliminating microglia/ macrophages, however they usually generate incomplete or transitory extirpation , influence perivascular , along with meningeal brain macrophages along with peripheral myeloid cells, as well asmight indirectly affect NSPC proliferation in addition to survival [206]. Correspondingly, approaches used to hamper NSPCs in vivo canonically influence other dividing glial , along with progenitor populations. Resultantly , changes in adult neurogenesis found in such models do not possess the capacity of getting ascribed unquestionably to microglia versus other macrophage populations or to NSPCs themselves, buttressing the requirement for refined,cell-type–particular genetic and chemogenetic strategies to define etiological associations .

Not all immune affects amongst the neurogenic niche are inimical [152]. Signals for instance TGF-β, IL-10, IGF-1, as well as CX3CL1 are escalatingly acknowledged in the form of factors which confer protection which possess the capacity of maintenance or restoration of neurogenesis as well [207]. However, if such mediators work in aniche- particular fashion along with the manner their diminishing assist in age- correlated collapse of neurogenic capability continues to be an uncharted query [208]. Clarification further is lacking if immune checkpoints or anti-inflammatory feedback loops normally confer protection to stem cells from inflammatory stress however fail with aging, leaving the niche susceptible to irreversible impairment [208].

The concept of a “niche immunome” has surfaced in the form of a robust parameter to decode the immune inflammatory signals which shape neurogenic niches [209]. Single-cell as well as spatial transcriptomic approaches now allow systematic profiling of the SGZ in addition to SVZ over age, displaying immune pathways which bulk parenchymal studies do not possess the capacity of rectification [148].

Such rectification is vital for differentiating local immune controlling of neural stem cells from generalized brain inflammation,along with for unearthing niche- susceptible particular susceptibilities which might define regenerative plausibility in aging [210. Closing neuroimmunology with regenerative neuroscience needs proceeding further than wide immunosuppression toward niche- particular arbitration [211]. Without exactitude of understanding into the immune circuits of the SGZ along with SVZ, treatments, a) risk silencing signals that confer protection b) whereas failing neurogenesis restoration [211]. Growing body of proof

from aging models illustrates that targeted manipulating of i) microglia, ii) T cells, or iii) cytokine pathways possesses the capability of rejuvenating neurogenic capability, buttressing the therapeutic attraction of restoration of local immune harmony [130].

Defining such mechanistic modes locates the niche immunome in the form of a vital frontier for exactitude arbitrations in brain aging [219].

### 3.5. Lacuna 5—Translational along with Cross-Species Disconnects

Maximum of our knowledge in reference to interactions amongst neuroinflammation as well as neurogenesis arises from rodent studies, however rodents vary earnestly from humans in i) biology, ii) lifespan, in addition to iii) milieu [212]. Mechanistic modes which result in rectification of neurogenesis or cognition in mice usually fail in clinical settings owing to i) molecular programs, ii) immune reactions , as well as iii) even circadian rhythms vary over species [101]. Human microglia illustrate i) unique transcriptional multifaceted nature, in addition to ii) adult neurogenesis itself is curtailed, along with controversial in humans contrasted to rodents [213]. This translational disengagement continues to be a core barricade, diminishing propagation from mechanistic modes understanding to treatments that are capable of counterbalancing age- associated cognitive reduction [212]. Rodents report sharply powerful adult neurogenesis, both in the i) hippocampal DG as well as in the ii) SVZ–olfactory bulb pathway, where thousands of new neurons are persistently produced in addition to integrated [214]. Contrasting humans possess absence of[important SVZ guided olfactory bulb 2nn neurogenesis ndisplayed 6 debatable] as well as. apparently diminishes with age [212]. Certain studies pointC continuation over thelifespan, whereas others debate it is practically eliminated in adulthood [111]. Such absence of lack of agreement complicates translational endeavors, in the form of approaches that authentically buttress rodent neurogenesis— for instance i) abundant milieu , ii) exercise, or iii) pharmacological arbitrations—might possess miniscule influence in humans [215]. In the absence of resolution of this debate, implementation of pro-neurogenic treatments clinically continues to be totally uncertain [216].

Human neuroinflammation digresses substantially from rodent models, escalating complexity translational endeavors [217]. Single-cell studies display that whereas core microglial programs are conserved, human microglia exhibit greater transcriptional multifaceted nature, arbitration distinct complement as well as phagocytic modules, in addition to a baseline preactivated state not delineated in rodents [213]. Additionally, human immune aging is shaped by i) lifelong infections, ii) systemic comorbidities,along with iii) lifestyle exposures lacking in laboratory animals, generatinge compounded inflammatory stress [116]. Such variations elicit botherations that arbitrations causing restoration of neurogenesis in mice, for instance i) exercise, ii) cytokine modulation, or iii) small molecules, might not provide analogous advantages in the aged human brain, buttressing the requirement for human-particular models in addition to biomarkers [218].

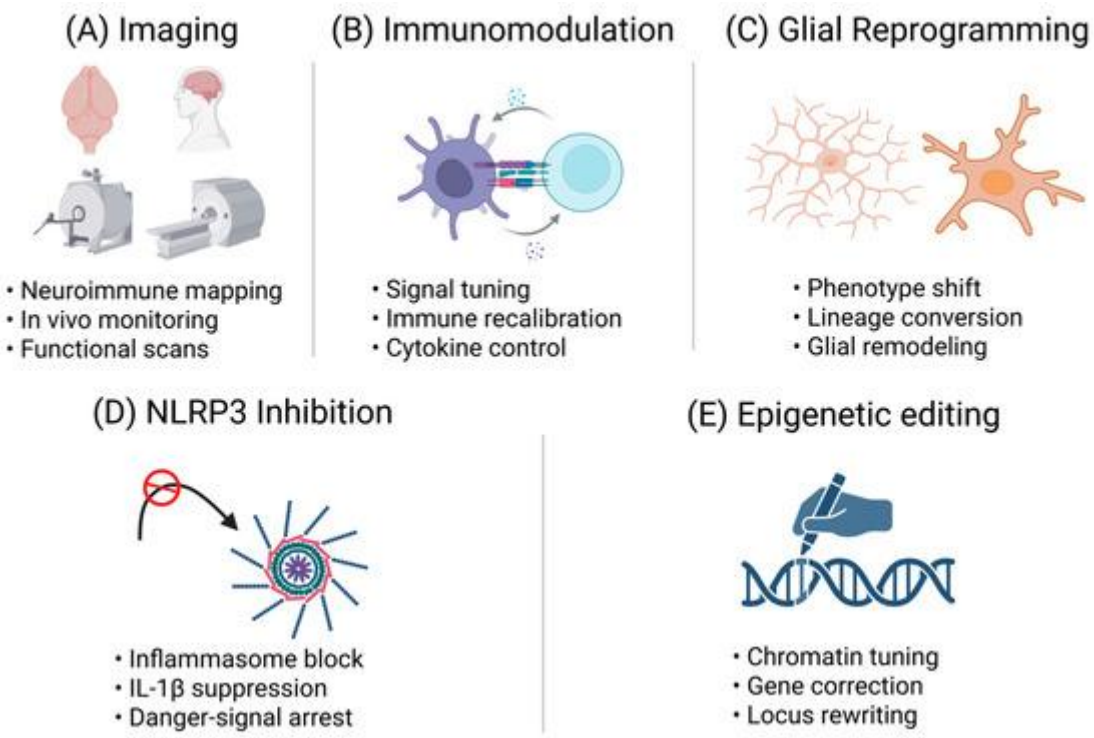
Bridging the translational lacunae needs models which catch the complexity of the human neuroimmune milieu greater sincerely in contrast to rodents [219]. Non-human primates provide intricate physiology, yet complementary systems for instance human brain organoids as well as induced pluripotent stem cell (iPSC)- obtained microglia–NSC co-cultures now yield extendable in addition to mechanistically appropriate gadgets [220]. Such podiums allow questioning of key pathways for instance NLRP3 or CX3CR1 in human- germane circumstances , while enabling controlled investigating of immunomodulatory as well as pro-neurogenic treatments [219]. By combining primate studies with organoid in addition to chip dependent -systems, investigators possess the capacity of forming clinically anticipative understanding which aggravate the translation of neuroimmune invention into arbitrations for aging- associated reduction [218].

With out human-particular understanding, immunomodulatory treatments risk working in the form of dampening tools, which either have failure in causing restoration of neurogenesis or causing disturbance imperative for immune working [140]. particular Closing species variations is hence irreplaceable. By improving targets amongst human germane systems, arbitrations possess the capacity of being fashioned to perpetuate or even rejuvenate neurogenic capability in aging, yielding a path to significantly rewire the brain's fate in clinical reality [221–223].

## 4. Approaches along with Surfacing Strategies to Connect the Lacunae

Subsequent to summarizing the above pivotal lacunae in knowledge here we detail five pivotal approaches in reference to tackling lacunae as well as manipulating the neuroimmune dialogue for therapeutic benefit.

Every subsection corresponds to a particular approach emphasized in the abstract (longitudinalneuroimmune imaging, niche-focused immunomodulation, glial subtype reprogramming, brain-penetrant NLRP3 hampering, as well as CRISPR- dependent based epigenetic editing). For every strategy,I will detail the idea , offer instances of present research or instruments , in addition to describe the manner it possesses the capability of aiding in filling one or more of the lacunae isolated in Section 3. I will also discuss on the feasibility along with timeline: which approaches are nearer-term vs. longer-term, and the manner they are capable of getting implemented in animal models or clinically (Figure 3).




**Legend for Figure 3.**

**Courtesy ref no-13-** Neuroimmune interventions—from mechanistic modes to therapeutic trajectory. (A) Imaging: Depicts neuroimmune mapping gadgets utilized for diagnostic as well as evaluation analytical purposes. The bullets refer to: Neuroimmune mapping—visualization of microglial in addition to inflammatory states; In vivo monitoring—longitudinal tracking of neurogenic, along with neuroimmune alterations; Functional scans—PET/MRI estimates associating immune activity to neurogenic output. Such methodologies evaluate, instead of modification of , biological pathways (B) Immunomodulation: Illustrates strategies that recalibrate maladaptive immune activity. The bullets indicate: Signal tuning—adjusting microglial or cytokine signaling thresholds; Immune recalibration— restoration of balanced immune tone; Cytokine control—targeted modulation of IL-1β, TNF, IL-6, or associated mediators [24,29]. (C) Glial Reprogramming: Mirrors strategies which switch glial cell identity or working . Bullets correspond to: Phenotype switch— switching microglia or astrocytes intoadoptive states; Lineage transformation —direct astrocyte-to-neuron or glia-to-neuron reprogramming; Glial remodeling—restructuring glial networks to escalate neurogenesis (D) NLRP3 hindering : Highlights repression of inflammasome-modulated inflammation. Bullets denote: Inflammasome block—direct hindering of NLRP3 assembly/activation; IL-1β repression—reduction in downstream pro-inflammatory cytokine liberation ; Danger-signal arrest— avoidance of upstream triggers guiding chronic activation (E) Epigenetic Editing illustrates locus- particular chromatin tuning gadgets. The bullets signify: Chromatin tuning—modifying histone or DNA accessibility at inflammatory loci; Gene correction—targeted repression or activation of disease- germane genes; Locus rewriting—durable transcriptional reprogramming without DNA cleavage This figure provides a modular overview of five neuroimmune arbitration strategies spanning monitoring, immune recalibration, glial engineering, inflammasome blockade, as well as epigenomic control. Together, they outline mechanistic entry points for perpetuating or restoring adult neurogenesis. Imaging methodologies working strictly in the form of diagnostic in addition to analytical gadgets instead of arbitrations, embracing asssessment of therapeutic actions on neurogenic, along with inflammatory dynamics. IL-1β, interleukin-1 beta; NLPR3, NLR family pyrin domain containing 3. Created in BioRender. Tanaka, M. (2026) https://BioRender.com/073ljub.

### 4.1. Longitudinal Neuroimmune Imaging

Whereas imaging methodologies for instance [18F] FLT-PET as well as TSPO-PET do not work in the form of therapeutic arbitrations, they offer pivotal diagnostic as well as monitoring capacities (Figure 3A).

Such gadgets track i) neurogenesis, ii) neuroinflammation, in addition to iii) treatment reaction in vivo, hence embracing , along with escalating the i) asssessment, ii) idealization , in addition to iii) stratification of true arbitrational approaches.

Longitudinal neuroimmune imaging is materializing in the form of a transformative strategy to tackle pivotal lacunae in our getting insight of brain aging [224]. It directly tackles Lacuna 3 by proceeding further than cross-sectional "snapshot" strategies, making dynamic monitoring of neurogenesis along with neuroinflammation over time amongst the same individual [225].

Such temporal resolution possesses the capability of displaying if surges in microglial activation takes place i)

prior to, ii) coincide with, or iii) subsequent to alterations in neural stem cell activity [224, 226]. Of equivalent significance , suchapproach advances lacuna 5 by yielding non-invasive, cross-species implementations via PET, magnetic resonance imaging (MRI), as well as two-photon microscopy [227]. By associating understanding of mechanistic modes from animal models to clinically germane biomarkers in humans, it buttresses translational bridges [227, 228].

Two-photon microscopy has modernized animal neuroimaging by making realtime, longitudinal finding of microglia–neuron crosstalks in the hippocampal neurogenic niche [229]. Utilizing chronic cranial windows, investigators possess the capacity of tracking the same cells over weeks, displaying events for instance i) synaptic trimming , ii) phagocytosis, as well as iii) manipulation of neural stem cell activity [229,230]. Fluorescent reporters in addition to genetic labeling approaches further escalates cellular specificity, aiding in exactitude mapping of immune–neural crosstalks[231]. Such methodologies yield unmatched understanding of mechanistic modes into the manner i) inflammation, along with ii) neurogenesis co-evolve, however they a)continue to be invasive, b)curtailed to small animals, as well as limited in imaging depth [232]. Although such restraints exist, animal imaging yields pivotal proof-of-concept results which stimulate translational approaches in humans [232, 233].

Positron emission tomography in addition to magnetic resonance imaging have become irreplaceable for longitudinal neuroimmune imaging, spanning both preclinical, along with clinical domains [234]. Translocator protein 18 kDa (TSPO)-PET is the maximum generated strategy for looking for activated microglia, however inference is impeded by i) low specificity, ii) multicellular expression, in addition to iii) genetic polymorphisms which influence ligand binding [235]. To tackle such limitations, empirical PET tracers for instance [^18F]FLT have been evaluated for labeling proliferating cells, with proof-of-concept studies illustrating that hampering tracer efflux makes determination of neurogenesis in vivo [234]. MRI offers a pivotal complement, providing high-resolution structural estimates for instance a) hippocampal atrophy as well as b) working connectivity readouts [236,]. Together, PET in addition to MRI generate a translational bridge, associating cellular-level events to human biomarkers , along with paving the way for therapeutic monitoring [237–240].

Next-generation imaging approaches are reshaping the manner we study neuroimmune dynamics.New PET tracers are being fashioned to discriminate amongst pro-inflammatory as well as anti-inflammatory microglial states, with favourable targets for instance P2 × 7R in addition to P2Y12R providing phenotype-particular resolution [241]. Other tracers have the objective of directly labelling neurogenic events or catch early astrocytic reactions [242,243]. Hybrid methodologies for instance PET/MR as well as dual-modal probes escalate spatial in addition to molecular exactitude, whereas computational strategies inclusive of radiomics, along with machine learning improve signal inference as well as anticipate results [244]. Incorporating imaging readouts with peripheral biomarkers from blood or cerebrospinal fluid (CSF) is an attractive multimodal criterion that possesses the capability of accentuating translation toward clinically actionable neuroimmune biomarkers [245].The future of longitudinal neuroimmune imaging has fulcrum on addressing pivotal technical in addition to, conceptual barricades [198]. New PET tracers are being generated to differentiate pro- along with anti-inflammatory microglial phenotypes or to directly look at neurogenic events, getting greater favourable particularly in contrast to TSPO- dependent gadgets [rev in 13]. Hybrid modalities for instance PET/MRI makes incorporation of i) molecular as well as ii) structural data, whereas iii) computational strategies inclusive of a) radiomics in addition to b) machine learning i) improving inference , along with ii) escalates anticipative power [246,247]. Pairing imaging with peripheral biomarkers from blood or CSF provides a multimodal approach that possesses the capability of transforming neuroimmune profiling, however attaining reliable, clinically translatable implementations would need aligned invention in addition to robust cross-species corroboration [198,248].

### 4.2. Niche-Concentrated Immunomodulation

Niche-concentrated immunomodulation acknowledges approaches which directly target the immune micromilieu of neurogenic areas for instance the i) hippocampal DG along with the ii) SVZ zone, providing a striking comparison to wide systemic immunosuppression [249] (Figure 3B). Such niches are apart from central to maintaining neurogenesis however further distinctly available for exactitude treatments [249]. Localized strategies are inclusive of a) intranasal administration of cytokines which possesses predilection to focus in i) ventricular areas, ii) biomaterials or iii) hydrogels engineered for maintenance of liberation of modulators, as well as absolute blood brain barrier(BBB)-permeable agents which accrue amongst neurogenic zones [250]. These approaches have illustrated that adapting immune signals at the region of neural stem cell activity possesses the capability of triggering neurogenesis whereas making systemic risksleast [249]. By concentrating arbitrations where they are maximum required, niche-targeted strategies offer a germane as well as clinically attractive pathway in reference to restoration of or perpetuating brain plasticity in aging in addition to disease [249,251]. Aged, along with inflamed neurogenic niches usually enroll CD8+ T cells as well as monocytes which liberate interferon-γ in addition to other hampering factors, directly i) repressing stem cell proliferation, along with ii) neurogenesis [148]. Neutralizing such inimical impacts has surfaced in the form of an attractive approach to confer protection to niche wholeness [252]. Strategies are inclusive of i) avoidance of immune cell entry with antibodies targeting adhesion molecules for instance CD44, or dampening their actions a) via cytokine neutralizers for instance IL-8 blockade. Empirical work illustrates that anti-inflammatory agents, inclusive of i)

indomethacin in addition to ii) minocycline, possess the capacity of perpetuating hippocampal neurogenesis at the time of inflammatory damages, buttressing the therapeutic plausibility of immune blockade [ 253]. Whereas systemic immunosuppression risks wide deficiencies, curtailing such approaches to the niche possesses the capability of selectively ameliorate, hampering signaling without causing dysfunctional host defenses [148]. These concentrated manipulation provides a germane pathway to counter age along with disease- correlated immune pressures whereas perpetuating the regenerative capability of the brain [148].

Escalating pro-neurogenic immune signals portrays a complementary approach to blocking inimical guides, with the objective of augmentation rather than reparative pathways amongst neurogenic niches [152]. Slanting microglia toward an "M2-like" phenotype through i) IL-4, ii) IL-13, iii) TGF-β mimetics, or iv) nanomaterial-based modulators has shown proof-of-concept advantages, improving neurogenesis in models of i) aging, ii) injury, as well as iii) neurodegeneration [254]. Further than immune sloping , engineered astrocytes or transplanted neural stem cells possess the capacity of beingprogrammed to liberate protective cytokines in addition to trophic factors, generating self-sustaining pro-regenerative feedback loops [255]. Biomaterials, along with hydrogels further expand such strategies by offering sustained, localized liberation of immune modulators amongst the hippocampus or SVZ [256]. Such approaches capitalize on the distinct availability of neurogenic zones to reprogram niche immunity from amongst [152]. By strengthening protective cues locally, instead of relying on systemicdelivery , treatments might greater efficaciously counter the age- associated decrease of neurogenesis while making inimical immunerepression least [152].

Implementing niche-concentrated immunomodulation needs tackling meaningful technical botherations however further opens considerable translational means [104, 257]. Precision administration systems for instance concentrated ultrasound possesses the capability of transitorily opening theBBB in hippocampal or SVZ sites, making local delivery of i) gene vectors, ii) cytokines, or iii) antibodies with diminished systemic spillover [258]. Engineered stem cell grafts or EVs provide additional routes in reference to maintenance of protection conferring immunomodulation directly within the niche, whereas gene therapy vectors possess the capacity of being attuned for long-term expression of pro-neurogenic signals [259]. Hurdles continues to be present, inclusive of attaining administration precision , with maintenance of therapeutic endeavors, as well as assisting in multifaceted nature across neurogenic zones [211]. Such accounting brings intricately to Lacuna 1, emphasizing in variable microglial areas, in addition to Lacuna 5, highlighting cross-species disengagement which escalates translation complexity [211]. By incorporating novel gadgets with human-germane models, niche-concentrated immunomodulation materializes in the form of a therapeutic bridge, converting understanding of mechanistic modes into exactitude approaches to rejuvenate neurogenesis in aging brains [211].

### 4.3. Glial Subtype Reprogramming

Glial subtype reprogramming portrays a bold therapeutic archetypal in which resident
glia are reconfigured to cultivate neural healing and adult neurogenesis [260] (Figure 3C). Two major approaches define this arena. Phenotypic reprogramming concentrates on restoration of impaired microglia or astrocytes to neuroprotective states, for instance by hampering inflammatory series or facilitating interactions cross-talk that favors protective cytokine release [261]. Lineagereprogramming goes further, converting astrocytes into neurons or neural progenitors through transcription factors for instance such as NeuroD1, DLX2, or Neurog2, or with small-molecule cocktails possesses the capability of triggering neuronal fates in vivo [262]. Collectively , such strategies seek to remodel the neurogenic niche, neutralize age- associated decline, as well as produce innovative vistas for brain rejuvenation rooted in cellular plasticity [257].

Phenotypic reprogramming of microglia has appeared in the form of a compelling approach in reference to restoration of neurogenic plausibility amongst the hippocampal niche [263]. Central to this strategy is the hampering of NF-κB in addition to related inflammatory series , that guides the liberation of cytokines whichrepress neural stem cell proliferation [264]. Pharmacological arbitrations for instance indole obtained, natural substances for instance mangiferin or costunolide,, along with small molecules targeting PI3K–Akt or Nrf2 signaling have successfully diminished proinflammatory activity whereas facilitating anti-inflammatory/trophic microglial programs (usually executed by IL-4– associated signatures) [138]. Correspondingly, exosome- dependent administration of miR-124 or growth factors for instance FGF1 rejuvenated microglial transcriptomes and escalated neurogenesis [rev 13]. Empirical corroborat ion illustrates that such arbitrations apart from blunting pathological inflammation but further refines hippocampal neurogenic output, resulting in cognitive as well as behavioral recovery in stress, injury, in addition to neurodegenerative models [263].

Lineage reprogramming of astrocytes has revealed an exceptional plausibility to regenerate neurons amongst injured or aged brains [264]. Advent of studies illustrate that transcription factors for instance i) NeuroD1, ii) DLX2, or iii) Neurogenin-2 possess the capacity of directly transforming reactive astrocytes into working neurons in vivo, with newly produced cells incorporating into local circuits along with restoration of behavioral working subsequent to injury or stroke [262]. Complementarystrategies utilize cocktails of small molecules to reprogram astrocytes into neurons or progenitor-like cells without viral vectors, providing a greater clinically favourable route [265]. Both genetic as well as chemical approaches have generated proof-of-concept corroboration that even reactive astrocytes in diseased or inflamed circumstances possess the capacity

of getting redirected toward a neuronal fate [266]. Such advancements point that lineage reprogramming might on a certain day amplify or replace lost neurogenesis, converting astrocytes into reservoirs of neuronal replacement [267].
Glial subtype reprogramming offers a bold approach to overcome Gap 1, the challenge of variable microglia according to site, in addition to Gap 2, the impact of inflammasome-guided epigenetic changes [35]. Arbitrations by restoration of homeostatic or neuroprotective microglial states, negate hampering cytokine series whichrepress neural stem cells [269]. Simultaneously, lineage reprogramming of astrocytes into neurons or progenitors escalates the neurogenic reservoir, directly reimbursing for age- associated diminishing [251]. Such double action both ameliorates maladaptive immune signaling, along with buttresses neuronal output, reframing glia not as barricades however in the form of therapeutic substrates for rejuvenating neurogenic niches [270].

Glial subtype reprogramming poses frightful however conquerable translational botherations [270]. Accuracy of administration continues to be of pronounced importance, in the form of viral vectors as well as gene editing gadgets present risks of off-target actions, immune reactions , in addition to unregulated proliferation [271].

The multifaceted nature of niches adds further complicated nature, demanding circumstances -sensitive approaches instead of indiscriminate arbitrations [272]. Novel modalities for instance i) CRISPR-based controlling, ii) hydrogel-rationed administration systems,along with iii) inducible gene circuits yield vistas for safer, greater regulated reprogramming [273]. Eventually , such strategy delineates a bold therapeutic frontier: the plausibility to "rewrite" the aging brain's fate by creating neurons from glia in addition to restoration of embracive immune states amongst neurogenic niches [260].

### 4.4. Brain-Penetrant NLRP3 Inflammasome hampering agents indicated

The NLRP3 inflammasome has materialized in the form of a central coordinator of chronic neuroinflammation, with microglial activation guiding maintained liberation of IL-1βwhich disturbs neural stem cell working along with causes dysfunctional neurogenesis [274] (Figure 3D). Whereas systemic hampering of such pathway illustrates anti-inflammatory favour, the unique botheration in brain conditions lies in attaining efficacious repression amongst the central nervous system (CNS) [275]. Small-molecule hampering agents possess the capacity of crossing the BBB, for instance nlrp3 inflammasome hampering agent mcc950 (MCC950) as well as newer candidates for instance i) NT- 0796 or ii) ASP0965, mirror an invention of class [275]. By directly targeting microglial inflammasome actions in situ, such substances tackle age- in addition to disease- associated priming of neuroinflammation which preserves i) cognitive diminishing , along with ii) aggravates neurogenic failure [276].

MCC950 has served in the form of the archetypal NLRP3 hampering agent , illustrating constant capacity of crossing the BBB as well as mitigates microglial activation across variable models of stress, injury, in addition to neurodegeneration [277]. By suppressing caspase-1 activation , along with IL-1β release, it perpetuates neural progenitor proliferation as well as attenuate cognitive diminishing in circumstances for instance i) AD, ii)) stroke, iii) traumatic brain injury (TBI), along with iv) depression-like states [278]. Constructing on such fundamental, innovative products for instance NP3-253 in addition to innovative bicyclic scaffolds have been fashioned for improved CNS penetration, stability, along with potency[279]. Preclinical studies with such substances validate that inflammasome hampering confers protection to hippocampal neurogenesis, buttressing the therapeutic attractiveness of such mechanistically targeted strategy [280].

New brain-penetrant NLRP3 hampering agents for instance NT-0796 as well as BGE-102 are switching into early clinical trials, representing a vital step in translating inflammasome biology into treatment [275]. Such substances illustrated strong CNS exposure in addition to have been illustrated to decline neuroinflammatory biomarkers in humans, yielding an attractive route in reference to arbitration in age- associated cognitive diminishing , along with mild cognitive dysfunction [275,281]. By disturbing IL-1β–guided feedback loops, they directly address lacuna 2, mitigating inflammasome guided epigenetic changes which lock microglia into pro-inflammatory states [282]. Simultaneously , their clinical generation talks to lacuna 5, bridging preclinical insights with druggable, human-germane approaches with the objective of rejuvenating neurogenic niches [283].Chronic NLRP3 activation in microglia apart from guidedrives IL-1β liberation however further imprints maladaptive epigenetic programs, inclusive of hypomethylation of inflammatory promoterswhich maintained reactivity. These "trained" states preserves neurotoxic signaling, causes dysfunctional neurogenesis, as well as cherish astrocytic impairment [284–286]. Hampering agents for instance MCC950 in addition to next generation brain-penetrant substances possess the capacity of disturbing such loop, blunting acute cytokine generation whereas cautiously reprogramming microglial memory toward a lesser inflammatory phenotype [286–288]. Such deeper understanding of mechanistic modes expands their significance further than transitory barricade, implying that inflammasome hampering might result in restoration of an embracive niche by stabilizing microglial identity along with obliviating epigenetic brakes on neurogenesis [190,289,290].

Whereas brain-penetrant NLRP3 hampering agents possess robust therapeutic attractiveness , botherations continue to be in orchestrating effectiveness with safety [291]. Risks are inclusive of i) off-target immunosuppression,

ii) unsure timing of arbitration , as well as iii) restricted information of long-term actions [291]. Refining specificity

through i) next-generation scaffolds, ii) selective inflammasome modulators, in addition to iii) combinatorial, biomarker- guided approaches possesses the capability of attenuating such botherations [292]. Eventually,NLRP3 hampering delineates one of the maximum concrete near-term pharmacological routes in reference to rejuvenating the neurogenic niche, translating understanding of mechanistic modes on inflammasome guided pathology into clinically actionable treatments for aging , along with neurodegeneration [293].

### 4.5. CRISPR- Dependent Epigenetic Editing

CRISPR- dependent epigenetic editing tackles catalytically inactive Cas9 (dCas9) fused to effector domainswhich change chromatin or DNA methylation, making locus- particular controlling of gene expression without installation of double-strand breaks [294] (Figure 3E). This discriminates it from canonical genome editing by aiding in reversible, non-mutagenic arbitrations [294]. For instance , dCas9-DNMT3A or DNMT3A/3L fusions possess the capacity of depositing methylation at promoters to quieten inflammatory genes, while dCas9-TET1 possesses the capability of triggering targeted demethylation to reactivate quietened loci for instance i) Oct4 or ii) Fgf21 [295]. Extra conformations, inclusive of KRAB- or Ezh2-dCas9 fusions, causes accrual of repressive histone marks, whereas SunTag-TET systems augment demethylase enrollment for robust activation [296]. Collectively, such gadgets provide unparalleled exactitude in modulating immune as well as neurogenic pathways at the epigenetic level [294].

CRISPR- dependent epigenetic editing directly addresses lacuna 2 by enabling the reversal of maladaptive methylation states in neural as well as immune cells shaped by aging or chronic inflammation [295]. For instance , targeting dCas9-DNMT3A to the IL1β promoter in aged microglia possesses the capability of restoration of quietening via re-methylation, hence diminishing chronic inflammatoryguide [297]. On the other hand, dCas9-TET1 applied to neurogenic loci for instance BDNF or Oct4 possess the capacity of obliviating age- stimulated suppression in addition to reactivate transcription, reinstating neurogenic plausibility in stem cells [295]. Proof-of-concept studies with Yamanaka factors or partial reprogramming corroborate that rejuvenating epigenetic marks restores neurogenesis as well as cognitive capability in aged niches [259]. Apart from transitory cytokine barricade , such approach reprograms cellular memory itself, providinglong lasting restoration of youthful transcriptional states in addition to opening innovative vistas for neuroregenerative treatment [298].

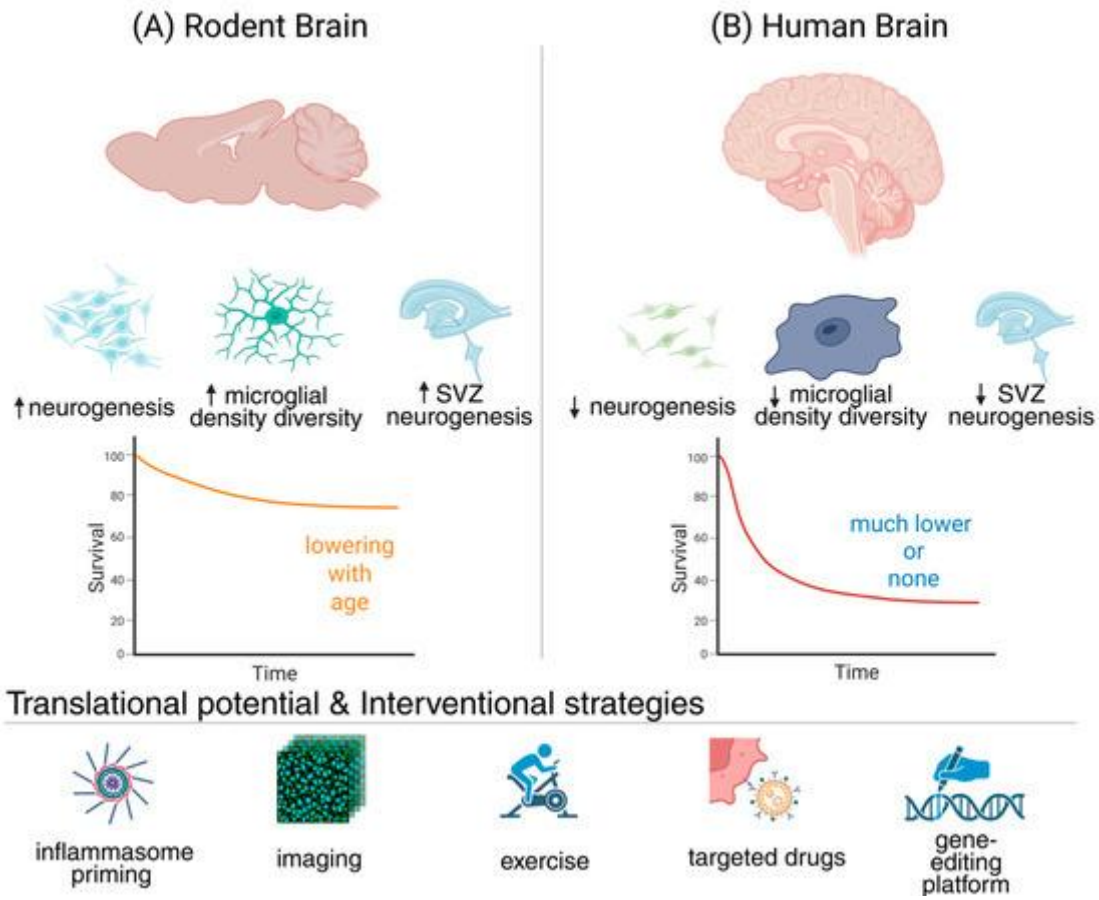
Preclinical studies emphasizes CRISPR-dependent epigenetic editing in the form of a multiskilled podium to reshape neuronal along with immune gene expression without installation of DNA breaks [299].In tauopathy models, dCas9-p300 activation of Gad1 caused rectification of synaptic hampering as well as cognition, whereas targeted methylation of the APP promoter in Alzheimer's mice declined amyloid pathology in addition to diminishing memory. CRISPRoff approaches have generated heritable transcriptional memory as well, illustrating maintained controlling over divisions [299]. In immune cells, epigenetic reprogramming stabilized lineage-particular expression, buttressing long persistence [300]. Theorizing, sustenance of neurotrophin expression in aged neural stem cells or quietening astrocytic inflammatory mediators possesses the capability of rejuvenating neurogenic niches [301]. By making i) exactitude , ii) long lasting, along with iii) programmable regulation of maladaptive states, CRISPR epigenetic editing directly tackles lacuna 5, providing a forward-lookingapproach to translate understanding of mechanistic modes into treatments for neurodegeneration as well as cognitive diminishing [299].

Translating CRISPR- dependent epigenetic editing into the brain faces menacing hurdles, with delivery working in the form of the maximum recent challenge [302]. Viral vectors for instance adeno-associated virus (AAV)s provide long lasting expression however risk insertional mutagenesis along with immunogenicity, while nonviral podiums for instance i) nanoparticles, ii) nanocapsules, as well as iii) engineered peptide coatings promise safer, localized delivery however continues to be under generation [303]. Of equivalent significance is the requirement to guarantee locus specificity, in the form of off-target chromatin remodeling possess the capacity of launching unanticipative in addition to long lasting actions [296,297,299]. Even with such risks, incremental advancements in vector design as well as precision editing suggest that long lasting,brain-targeted arbitrations are achievable [301]. In the long lasting duration, CRISPR epigenetic editing might may assume a revolutionary therapeutic technology, which possess the capacity of indelibly resetting maladaptive cellular states, rejuvenating neural stem cell plausibility , in addition to result in maintenance of neurogenesis well into aging [302].

## 5. Corresponding viewpoints: Human vs. Animal Models

Getting insight in the manner the rodent as well as human data correspond —or differ—is imperative for exploring the translational germaneness of neurogenesis along with neuroinflammation research [111].

Animal models yield exactitude in reference to mechanistic modes , providing corroboration for continuous however declining neurogenic activity in addition to for microglial switching which shape brain plasticity over the lifespan [215]. Human studies, however, display more absence of reassurance, with additional complexity by differences of technologies utilized along with ethical hindrances[rev in 13]. By comparing such viewpoints , we possess the capacity of isolating both the strengths as well as drawbacks of each strategy, setting the stage for a greater intricate exploration of adult hippocampal neurogenesis over species [111 ] (Figure 4).




**Legend for Figure 4.**

**Courtesy ref no-13**- Comparative overview of neurogenic capability in rodents as well as humans. Cross-species comparisons are complicated by age-matching in addition to sampling circumstance: plethora of rodent datasets obtain from young adult animals, whereas human evidence usually depends on post-mortem tissue from olderpersons with diverse comorbidity , along with peri-mortem factors. As per that, the schematic highlights directional tendencies as well as differences of technologies display more absence of reassurance , not direct quantitative equivalence of neurogenic 'capacity' amongst species. (A) Rodent Brain: Rodents sustain germanely greater quantities of adult neurogenesis over the lifespan, embraced by variable microglial populations as well as sustained subventricular zone (SVZ) neurogenic activity. This are inclusive of robust DG in addition to SVZ neurogenesis in young adulthood, along with estimable continuation into aging, consistent with preclinical neurogenic literature [1,2,3]. Rodent microglia illustrate escalated phenotypic variability in addition to clear age-associated priming [116,165]. Survival curves exhibit the well- displayed progressive diminishing in neuronal continuation with age, whereas maintenance of observable neurogenic capability. (B) Human Brain: Humans illustrate extensively diminished adult neurogenesis, reduced microglial variability, along with curtailed or absent SVZ- obtained neuronal generation . Human studiesdisplay much lower baseline neurogenic output, debated continuation in older age groups, along with curtailed microglial multifaceted nature contrasted with rodents [1,2]. Human microglial transcriptional profiles further exhibit lesser variable aging directionsgermane to rodent profiles .The survival curve delineates least or near-zero long-term survival of adult-born neurons over adulthood. Translational plausibility & arbitrational approaches: The lower panel emphasizes mechanistic targets as well as candidate arbitrations with therapeutic germaneness . Inflammasome priming hampering agents: embraced by preclinical NLRP3-blocking agents for instance NT-0796, MCC950, BGE-102 for longitudinal neuroimmune monitoring: FLT-PET, TSPO-PET, in addition to hybrid PET/MRI Exercise- guided neurogenic escalation: Rodent, along with translational exercise actions on neurogenesis as well as inflammatory pathways Targeted immunopharmacology: Cytokine-level immunomodulation from IL-1β/TNF- guided models [24,29]. Gene-editing platforms: CRISPR- dependent epigenetic or transcriptional tuning gadgets SVZ, subventricular zone. Created in BioRender. Tanaka, M. (2026) https://BioRender.com/eqw4kap.

### 5.1. Adult Neurogenesis: Rodents vs. Humans

Adult rodent studies have firmly generated that hippocampal neurogenesis is robust in youth as well as drop with age, however it does not ever get fully eliminated [98]. Bromodeoxyuridine labeling in addition to lineage tracing exhibit that new granule cells keep getting produced persistently in the DG, despite proliferation rates declines drastically with aging, from approximately three percent of granule cells in young adults to under ½% in old animals [304]. Despite under stressors for instance ischemia or stroke, aged rodents preserve the capability for damage stimulated neurogenesis,with locally activated neural stem , along with progenitor cells materializing in peri-infarct areas, despite their effectiveness as well as neuronal differentiation are diminished [305]. Complementary observations in human stroke in addition to ischemic pathology indicate that neurogenic progenitors , along with stem-like cells possess the capacity of further getting mobilized amongst or neighbouring to damaged areas, implying that endogenous stem cell pools continues to be minimally partially reprogrammable as well as possess the capacity of aiding in capable of structural healing , in the aged brain as well [270,273]. Such observations validate a continuous, despite though declined, neurogenic reservoir over the lifespan [98].

In humans, validation for adult hippocampal neurogenesis continues to be sharplydivided [306]. Boldrini et al.[307], from Kuhns group.[307], documented thousands of immature neurons continuing in older adults as well, whereas Sorrells et al.[307],from Kuhns group debated that new neurons are practically missing further than childhood [307]. Maximum of such variability arises from methodological factors: i) antigen preservation, ii) fixation times, in addition to iii) tissue sampling pivotally estimate whether markers for instance i) doublecortin (DCX) or ii) polysialylated neural cell adhesion molecule(PSA-NCAM) areestimable [107]. Reviews highlight that small variations in processing possesses the capability of providing converse conclusions, making agreement tough [110]. The debate continues, with maximum in agreement that i) technical vigour, ii) standardized protocols, in addition to iii) multimodal strategies are imperative in reference to resolution of such debate as per Kempermann et al.[308].

### 5.2. Microglial States Across Species

Rodent studies have yielded a thorough atlas of microglial aging, displaying stable transcriptional as well as metabolic switching which define an “inflammaging” signature [309]. Single cellRNA sequencing across the mouse lifespan uncovers plethora of microglial states, with aging delineated by potentiated chemokine expression in addition to reprogramming of metabolic pathways[rev 13]. An especially sharp characteristic is the materialization of lipid droplet–accrual microglia, that documented i) aberrant phagocytosis, ii) exacerbated cytokine liberation along with iii) altered lipid metabolism [11]. Proteomic as well as transcriptomic evaluation further illustrate reduced homeostatic signaling, escalated glycolysis, in addition to overlap with disease-associated microglia (DAM) [310]. Taken together, such observations generate aged rodent microglia in the form of i) pro-inflammatory, ii) metabolically reprogrammed, as well as iii) primed for maladaptive reactions to stress or damage [309].

Human microgliadocument both sharp overlaps with rodents in addition to, unique aging trajectories that underscore species divergence [312]. Transcriptomic studies reveal that while a conserved core program exists, humans show distinct controlling of i) adhesion, ii) cytoskeletal, along with iii) complement- associated genes, beside greater transcriptional multifaceted nature with age [213]. Unlike rodents, aged human microglia usually generate dystrophic morphologies as well as changed reactions to neurodegeneration [101]. Nevertheless, shared properties materialize: chronic systemic inflammation aggravates microglial aging over species, as well as both mice in addition to humans illustrate escalated T cell infiltration in the SVZ zone, reshaping the neurogenic niche [312].

Such corresponding along with variabilities emphasize the significance of corresponding viewpoints for translational germaneness (Figure 4A). ,

### 5.3. Inflammatory Pathways along with Neuroimmune Crosstalk

Rodent studies have documented the manner inflammasome priming in addition to glial interactions shape neurogenic outcomes in aging as well as disease [313]. Activation of the microglial NLRP3 inflammasome e guides the transformation of astrocytes into complement-enriched reactive programs (usually labelled “A1-like” in rodent literature, with recognized limits to this binary), repressing neurogenesis along with causing dysfunctional cognition, whereas genetic elimination of Nlrp3 or therapy with hampering agents for instance MCC950 causes restoration of working [314]. Correspondingly, interferon-gamma (IFN-γ)–primed microglia cause dysfunctional neural stem cell proliferation, an action reversible by janus kinase/signal transducer and activator of transcription 1 (JAK/STAT1) barricade [31].

Tri-culture models corroborate that microglia–astrocyte crosstalks amplify inflammatory series, whereas mitochondrial dysfunction further exacerbates NLRP3 action[146]. Such observations reinforce the manner rodent systems which are manipulable by exactitude represent pathways where inflammation restricts hippocampal neurogenesis.

In humans, evidence for inflammasome activation is basicallyindirect, obtained from i) Postmortem evaluation , ii)CSF biomarkers, iii) surfacing imaging studies [315]. Escalated IL-1β, IL-18, as well as inflammasome proteins for instance ASC , along with caspase-1 have been documented in neurodegenerative disease(NDD) in addition to TBI, usually associating with robustness or result [316].

Immunohistochemistry illustrates co-localization of NLRP3 with glial markers in Alzheimer's tissue, while iPSC- obtained microglia associate genetic risk factors to inflammasome priming[317]. Nevertheless, inference is complicated by timing, chronic disease progression, in addition to comorbidities, making etiological interpretation substantially lesser simpler in contrast to in regulated rodent experiments [315] (Figure 4B).

### 5.4. Arbitration Effectiveness along with Translational Preparedness

Rodent studies provide strong corroboration that lifestyle as well as empirical arbitrations possess the capacity of escalating neurogenesis in addition to perpetuate cognition well into aging, along with disease [318,319].Aerobic exercise diminishes microglial inflammasome activity through irisin signaling, restoring hippocampal neurogenesis as well as memory in Parkinson's models [320]. Environmental abundance , with or without exercise, constantly improves learning in addition to diminishes anxiety like behaviors, whereas further limiting aberrant neurogenesis subsequent to stroke [321]. Mechanistically, such actions stem from i) diminished inflammation, ii) epigenetic reprogramming, along with iii) escalated plasticity across hippocampal subareas [322]. iv) Direct modulation, for instance BDNF overexpression or sodium lactate administration, replicate the advantages of abundance as well as exercise, buttressing their etiological associations to neurogenesis in addition to cognitive adaptability [323].

In humans, lifestyle arbitrations for instance i) exercise, ii) cognitive engagement,along with iii) diet constantly improve cognition as well as brain health, however their association with neurogenesis continues to be indirect, interpreted from alterations in neuroplasticity in addition to, neurotrophic signaling instead of direct cellular confirmation [324]. Clinical trials of non-steroidal anti-inflammatory drugs (NSAD)in AD have been frustrating , with large-scale meta-analyses illustrating no significant advantages as well as emphasizing inimical processes as well [325]. This discrepancy with epidemiological associations reinforces the complicated nature of timing along with target specificity in human disease [326]. More selective approaches, specifically NLRP3 inflammasome hampering agents, portray an surfacing arena with powerful mechanistic germaneness, however translation is still in its budding stage , waiting for corroboration of effectiveness in addition to safety in controlled human trials [291].

### 5.5. Closing the Lacunae : Models, Ethics, along with Future Outlook

Rodent models allow invasive modulations for instance i) ablation, ii) lineage tracing, as well as iii) precise genetic editing, approaches which are foundationally curtailed in humans due to ethical in addition to practical barricades [327]. Human studies rather depend on i) observational fashions, ii) neuroimaging, along with iii) pharmacological arbitrations, yielding indirect however clinically germane understanding [328]. Post-mortem tissue yields imperative molecular detail however further catches late-stage as well as peri-mortem bafflers . Complementing this, living human brain tissue obtained at the time of neurosurgery enables direct assessment of microglial morphology in addition to behavior in viable adult tissue, yielding an occasional hurdle amongst rodent dynamics as well as human reality. Integrating such datasets would be capable of sharpening the manner we infer 'dystrophy,' surveillance, as well as contact behavior in human microglia [329]. While nonhuman primates in addition to organoid- dependent chimeras aid navigating lacunae , their utility is further restrained by ethical scrutiny along with probability [330,331]. Sequentially, translational propagation depends on incorporating exhaustive detail of mechanistic modes from animal work with non-invasive, ethically thorough human research approaches which cause improvement diminish, along with cause replacement of invasive experimentation where feasible [332].

Future propagation would be based on combining advancement of imaging as well as circulating biomarkers with humanized models which incorporate microglia into brain organoids [333]. These systems aid dynamic watching of neuron–glia interactions , catch human-particular inflammatory signatures, in addition to yield a podium for investigating therapeutic approaches [334].

Rodent models continues to be irreplaceable for dissecting mechanistic modes as well as enabling invasive manipulations which do not possess the capacity of getting conducted in humans [335]. Nevertheless, breakthroughs need to escalatingly concentrate on organoid-based as well as biomarker- guided strategies, guaranteeing translation catches the complicated nature of human neuroimmunity whereas preserving the clarification of mechanistic modes yielded by animal studies (Figure 4).

## 6. Incorporating Mechanistic modes with Therapeutics: Toward Rewiring theAging Brain

The intersecting of deeper understanding of mechanistic modes with therapeutic invention marks a critical frontier in endeavors to reshape the time period duration of brain aging [336,337]. Instead of viewing neurogenesis reduction in addition to neuroinflammation in the form of inescapable benchmarks of senescence, surfacing research documents them in the form of modifiable events which possess the capacity of getting recaliberated via exactitude arbitrations [21]. By coordinating exhaustive information of i) inflammasome signaling, ii) microglial states,along with iii) epigenetic controlling with translational gadgets for instance i) advanced imaging, ii) targeted drugs, in addition to iii) gene-editing podiums, we start charting a roadmap for reprogramming adaptability. This section takes into account the manner such once- dissimilar approaches might synergize, yielding realistic short-term goals along with bold long-term insights for postponement or even reverting cognitive reduction [338,339].

### 6.1. Exploiting Mechanistic modes Lacunae as Options

Lacunae in translation must not be visualized in the form of hurdles however in the form of guidance markers driving advent [340]. Comparable research amongst animal models as well as humans constantly reveals mismatches in pathology, timing, in addition to reaction , however these very mismatches emphasize the manner innovation is feasible as well as utilize opportunities for invention [341]. Drawbacks in rodents have stimulated the generation of i) humanized organoids, ii) large animal models, in addition to iii) network- dependent strategies which catch human complicated nature in a greater advantageous manner [342]. In such manner, each isolated lacunae suggests a therapeutic or theoretical option, in addition to the following approaches might be looked in the form of direct reactions to such translational signposts [343].

A)Microglial multifaceted nature (Lacuna 1) yields greater than complicated nature ; it offers a parameter a) in reference to fashioning site -particular along with b) state-selective arbitrations [48]. Rodent studies have mapped disparate transcriptional states across i) age as well as ii) pathology, iii) whereas human transcriptomics validate that such subtypes are present however follow unique directions, driving translational antecedency [191,344]. B)Correspondingly , a) inflammasome- guided epigenetic controlling(Lacuna 2) surfaces in the form of a fertile ground for therapeutic invention. NLRP3 hampering agents(Strategy 4.4) as well as b) CRISPR- dependent epigenetic editing (Strategy 4.5) typify strategies which possess the capacity of resetting maladaptive inflammatory programs [291,345]. Therefore , what apparently is a translational drawback is concomitantly the germaneness for exactitude arbitrations which reprogram cellular states in aging brain niches [269]. C) Lacuna 3 emphasizes systemic impacts in the form of a pivotal axis where rodent in addition to human data intersect [346,347]. Parabiosis studies along with regulated inflammatory botherations in mice illustrate the etiological power of circulating factors to aggravate or reverse brain aging, b) whereas in humans such impacts are tracked indirectly via i) biomarkers, ii) immune profiling, as well as iii) neuroimaging [348].

D) Lacuna4 reframes modeling restraints in the form of a catalyst for discovery, guiding the generation of a) humanized organoids with microglia or b) vascular incorporation [349]. Collectively , such strategies shrink the translational length, aiding in rodent understanding of mechanistic modes to be associated with human germaneness as well as opening novel options for therapeutic invention [350,351].

E) Lacuna 5 represents the pivot from mechanistic modes to medicine, where understanding from animal models start to shape clinical option [343,352]. Rodent studies illustrate that i) targeting the NLRP3 inflammasome, ii) reinforcing neurotrophic signaling, or iii) trapping epigenetic editing possess the capacity of a) restoration of neurogenesis in addition to b) rescuing cognition, c) stimulating translational endeavors for instance i) NLRP3 hampering agents now moving toward human trials [176]. ii) Lifestyle dependent arbitrations likewise illustrate intersecting advantages, even if mechanistic modes vary over species [353]. Comparable viewpoints are a reminder of drawbacks however further emphasizes positiveness: every lacunae assumes a guidepost, suggesting directly to the therapeutic approaches possessing the maximum plausibility of rejuvenating neurogenesis in addition to overcoming cognitive diminishing [354].

### 6.2. Translational Roadmap

Longitudinal imaging possesses placement at the forefront of translational propagation, yielding a manner in reference to monitoring i) neuroinflammation along with ii) neurogenesis non-invasively over time [190]. i) Advancements in PET tracers, from a) second-generation TSPO ligands to b) newer targets for instance i) COX , along with ii) P2X7 receptors, offer a) greater attractive specificity as well as b) working understanding of mechanistic modes [191]. ii) Complementary multiparametric MRI strategies put spatial in addition to physiological circumstances, making incorporation with PET for enrichment of biomarker panels [254]. Nevertheless, strong clinical translation need a) robust standardization, b) multicenter capacity of replication, as well as c) careful association of imaging signals with d) cognitive outcomes [355]. Generating corroborated tracers in addition to balanced protocols would establish imaging in the form of a dependable bridge i) amongst understanding of mechanistic modes, along with ii) therapeutic monitoring [356].

Rodent studies have illustrated that i) intranasal delivery of EVs, ii) nanoparticles, or iii) viral vectors possess the capacity of manipulating microglial activation as well facilitating neuroprotection, as in addition to the botheration now exists in expanding such approaches to non-human primates [302]. Advances in engineered AAVs along with synthetic promoters already make selective targeting of glial populations, whereas improved capsid variantsdiminish peripheral exposure , off-target actions [357].B) Nonviral systems, for instance i) EVs as well as ii) lipid nanoparticles, add a) further resilience in addition to b) safety [161].

Pivotal cornerstones are inclusive of illustrating i) long-term safety, ii) replication capacity , along with iii) circuit specificity, iv) guaranteeing that reprogramming arbitrations translate efficaciously into clinically viable treatments [163,358].

NLRP3 hampering agents are switching from preclinical promise to clinical evaluation, with trials in AD now concentrating on i) safety, ii) dose idealization, as well as iii) early cognitive outcomes in the form of imperative benchmarks [295]. Small molecules for instance i) MCC950, ii) OLT1177, in addition to iii) JC124,beside materializing biologics, have constantly i) diminished neuroinflammation , along with ii) improved cognition in rodent models, as well as numerous are propagating into human investigations [160,283,359]. effectiveness Their success will hinge on demonstrating i) BBB penetration, ii) tolerability, in addition

to iii) biomarkercorroboration [286,295]. Looking ahead, combinatorial strategies pairing inflammasome hampering with lifestyle or behavioral arbitrations might escalate effectiveness as well as widen therapeutic germaneness [286].

CRISPR-based epigenetic editing is advancing rapidly in preclinical research, offering the unprecedented plausibility of rewriting maladaptive molecular memory at specific genomic loci [297]. Present endeavors center on administration approaches, with AAV vectors yielding robust CNS transduction as well as nanoparticles materializing in the form of safer, non-viral alternatives [360].

The vital botherations are attaining locus specificity, guaranteeing long lasting duration without irreversibility, in addition to ensuring least immune or off-target actions [361]. Such gadgets possess distinct attractiveness for manipulating inflammatory or neurogenic pathways directly at the epigenetic level, however clinical translation will depend on tackling safety, administration , along with regulatory hurdles with vigorous exactitude [297].

The future of translation lies in customizing arbitrations to individual neuroinflammatory and epigenetic panorama, switching further than one-size-fits-all strategies [362]. Stratifying patients through biomarker and pharmacogenomic profiling possess the capacity of could driving the choice of pharmacological, behavioral, or gene-based approaches, whereas combinatorial treatments might unlock greater synergy in contrast to single technologies [363]. Lifestyle programs possess the capacity of complementing NLRP3 hampering or epigenetic editing, and regenerative gadgets might be individualized for niche rectification [364]. The roadmap continues to be incremental, however every benchmark brings us intricate to clinically rejuvenating neurogenesis as well as perpetuating cognition across aging in addition to, disease [211,228].

### 6.3. Ethical and Clinical Considerations

Exactitude epigenetic editing possesses transformative therapeutic plausibility, however it brings meaningful safety botherations which does not possess the capacity of getting ignored [365]. CRISPR- dependent strategies risk unplanned off-target manipulations, unanticipatable time period course of alterations, as well as immune reactions stimulated by delivery vectors for instance AAV or nanoparticles [366]. In the CNS, even small mistakes might possess continuous actions, escalating botherations in reference to circuit stability in addition to, tumorigenesis [367]. Long-term surveillance would be essential to estimate postponed sequelae of editing [368]. Preclinical pipelines must hence arrange reversible, temporally regulated systems along with exhaustive off-target profiling prior to such approaches switch into first-in-human trials [369].

Glial reprogramming delineates one of the maximum stimulating borders in regenerative neuroscience, however its clinical translation is shadowed by earnest safety botherations [370].

Transformation of glia into neurons possesses the risks of i) aberrant network activity, ii) seizure induction,or iii) tumorigenesis if new cells fail toincorporate appropriately [269]. Appropriate synapticintegration as well as maintenance of circuit balance are hence of pronounced importance , owing to incomplete or unregulated transformation possesses the capability of causing destabilization of neural networks [371]. The promise of replacing lost neurons need to be judged against an ethical/moral duty to confer protection susceptible cases, guaranteeing that regenerative enthusiasm does not outpace vigorous safety in addition to ethical supervision [278]. Immune modulation in the aging brain poses an intense double-edged concern.Whereas repressing microglial overactivation or blunting inflammasome signalingmight cause restoration of plasticity as well as cognitive flexibility, escalated repression risks jeopardizing pathogen defense, escalating susceptibility to infection or cancer as well [372]. Calibrating such interventions in elderly patients hence requires a fine harmony amongst rejuvenation along with safety [372]. Stratification by immune competence, genetic background, in addition to comorbidities would be vital for diminishing inimicality [373]. Eventually, individualized immune arbitrations need to propagate with precaution , guaranteeing that therapeutic invention coordinates with the biological realities of aging immunity.

Preventive arbitrations in normal aging escalates complicated ethical dilemmas, specifically when the treatments under consideration possess extensive risks [374]. At what threshold does postponingg cognitive reduction accounts for invasive gene editing or immune manipulation inpersons without disease? Independence as well as informed consent must continue to be central, however both are concerns raised by uncertainty in anticipating advantages [374]. Societal challenges further stems, from medicalizing normal aging to buttressing unfairness in availability [374]. Defining clear thresholds of clinical risk versus plausible gain is hence imperative prior to avoidance of neuroenhancement possess the capacity of getting ethically endorsed.

Controlling pathways in neurodegenerative arbitrations vary considerably, with small molecules for instance NLRP3 hampering agents usually propagating greater swiftly in contrast to gene or cell-based treatments, that need complicated omission [294]. Designing trials whichcatch both safety in addition to significant results continue to be imperative [375]. Further than inimical processes , endpoints need to be inclusive of i) cognition, ii) neurogenesis biomarkers, along with iii) quality of life to illustrate true clinical germaneness [375]. Balanced protocols, long-term monitoring, as well as adaptive trial fashions designs would be vital [376]. Eventually, ethical rigor in addition to controlling farsightedness yield the backbone for translating scientific inventions into safe, responsible treatments [377].

## 7. Conclusions

Neurogenesis as well as neuroinflammation exist in continuous dialogue, shaping the manner the brain ages in addition to reacts to stress [12]. Earlier we have reviewed Genome Editing With the Utilization of CRISPR/ Cas 9 System for Evaluation and Treatment of Human Diseases&role of Brain organoids to fashion HumanModel of Neurological Disorders besides NLRP3 inflassome,brain metabolism with importance of astrocytes-OS with part of nuclear factor erythroid-2-related factor-2((Nrf2) /Kelch-like-epichlorohydrin (ECH)-associated protein 1 (KEAP1) in case of traumatic brain injury(TBI), neurodegenerative diseases(NDD) [67,378,379]. This review has emphasized that disturbing such dialogue inneurogenesis as well as neuroinflammation exacerbate diminishing cognition, whereas fine tuning it possesses the capability of perpetuating or causing restoration of cognitive adaptability as well. Mapping pivotal lacunae, along with coordinating them with targeted approaches yields a roadmap for arbitration [2]. The core message is clear: the neurogenic plausibility of the aging brain is not eliminated however continues to be accessible if the immune milieu is cautiously recalibrated . In late life as well, glia in addition to neural stem cells perpetuate extensive plasticity. Tackling such latent capability needs intersecting strategies, from modulating microglial states along with inflammasome signaling to applying epigenetic editing, gene therapy, as well as innovative imaging biomarkers [380,381]. Such approaches are greater than step- by step - advances; they delineate a switching in the manner we notionalize as well as try to reshape the brain's fate at the time of aging. The innovation in addition to importance of such strategies lie in their incorporative feasibility . By combining understanding of mechanistic modes with novel modalities, we are starting to look at the shapes of arbitrations that possess the capacity of postponing neurodegeneration in addition to confers protection to cognition. Joseph et al.further displayuse of Brain-Permeable PET Tracer for P2Y12 Receptor Imaging[382]. Thebotheration now is translation: i) impacting safety, ii) ethics, iii) along with rigorous trial fashioning into every step. iv) With continued interdisciplinary collaboration, the prospect of actively driving the neuroimmune dialogue toward healthier brain aging is amongst reachable [2,276].

## References


1. Boldrini, M.; Fulmore, C.A.; Tartt, A.N.; Simeon, L.R.; Pavlova, I.; Poposka, V.; Rosoklija, G.B.; Stankov, A.; Arango, V.; Dwork, A.J.; et al. Human Hippocampal Neurogenesis Persists throughout Aging. Cell Stem Cell 2018, 22, 589–599.e585.
2. Babcock, K.R.; Page, J.S.; Fallon, J.R.; Webb, A.E. Adult Hippocampal Neurogenesis in Aging and Alzheimer's Disease. Stem Cell Rep. 2021, 16, 681–693.
3. Anacker, C.; Hen, R. Adult hippocampal neurogenesis and cognitive flexibility—Linking memory and mood. Nat. Rev. Neurosci. 2017, 18, 335–346.
4. de Lima, E.P.; Laurindo, L.F.; Catharin, V.C.S.; Direito, R.; Tanaka, M.; Jasmin Santos German, I.; Lamas, C.B.; Guiguer, E.L.; Araujo, A.C.; Fiorini, A.M.R.; et al. Polyphenols, Alkaloids, and Terpenoids Against Neurodegeneration: Evaluating the Neuroprotective Effects of Phytocompounds Through a Comprehensive Review of the Current Evidence. Metabolites 2025, 15, 124.
5. Culig, L.; Chu, X.; Bohr, V.A. Neurogenesis in aging and age-related neurodegenerative diseases. Ageing Res. Rev. 2022, 78, 101636.
6. Toda, T.; Parylak, S.L.; Linker, S.B.; Gage, F.H. The role of adult hippocampal neurogenesis in brain health and disease. Mol. Psychiatry 2019, 24, 67–87.
7. Valero, J.; Bernardino, L.; Cardoso, F.L.; Silva, A.P.; Fontes-Ribeiro, C.; Ambrosio, A.F.; Malva, J.O. Impact of Neuroinflammation on Hippocampal Neurogenesis: Relevance to Aging and Alzheimer's Disease. J. Alzheimers Dis. 2017, 60, S161–S168.
8. Amanollahi, M.; Jameie, M.; Heidari, A.; Rezaei, N. The Dialogue Between Neuroinflammation and Adult Neurogenesis: Mechanisms Involved and Alterations in Neurological Diseases. Mol. Neurobiol. 2023, 60, 923–959.
9. Meszaros, A.; Molnar, K.; Nogradi, B.; Hernadi, Z.; Nyul-Toth, A.; Wilhelm, I.; Krizbai, I.A. Neurovascular Inflammaging inHealth and Disease. Cells 2020, 9, 1614.
10. Jurcau, M.C.; Jurcau, A.; Cristian, A.; Hogea, V.O.; Diaconu, R.G.; Nunkoo, V.S. Inflammaging and Brain Aging. Int. J. Mol. Sci. 2024, 25, 10535.
11. Marschallinger, J.; Iram, T.; Zardeneta, M.; Lee, S.E.; Lehallier, B.; Haney, M.S.; Pluvinage, J.V.; Mathur, V.; Hahn, O.; Morgens, D.W.; et al. Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. Nat.Neurosci. 2020, 23, 194–208.
12. Wendimu, M.Y.; Hooks, S.B. Microglia Phenotypes in Aging and Neurodegenerative Diseases. Cells 2022, 11, 2091.
13. Tanaka M.Neurogenesis and Neuroinflammation in Dialogue: Mapping Gaps, Modulating Microglia, Rewiring Aging. Cells 2026; 15: 78
14. Lawrence, J.M.; Schardien, K.; Wigdahl, B.; Nonnemacher, M.R. Roles of neuropathology-associated reactive astrocytes: A systematic review. Acta Neuropathol. Commun. 2023, 11, 42.
15. Clarke, L.E.; Liddelow, S.A.; Chakraborty, C.; Munch, A.E.; Heiman, M.; Barres, B.A. Normal aging induces A1-like astrocyte reactivity. Proc. Natl. Acad. Sci. USA 2018, 115, E1896–E1905.
16. Propson, N.E.; Roy, E.R.; Litvinchuk, A.; Kohl, J.; Zheng, H. Endothelial C3a receptor mediates vascular inflammation and blood-brain barrier permeability during aging. J. Clin. Investig. 2021, 131, e140966.
17. Elahy, M.; Jackaman, C.; Mamo, J.C.; Lam, V.; Dhaliwal, S.S.; Giles, C.; Nelson, D.; Takechi, R. Blood-brain barrier dysfunction developed during normal aging is associated with inflammation and loss of tight junctions but not with leukocyte recruitment.Immun. Ageing 2015, 12, 2.
18. von Bernhardi, R.; Eugenin-von Bernhardi, L.; Eugenin,

J. Microglial cell dysregulation in brain aging and neurodegeneration. Front. Aging Neurosci. 2015, 7, 124.
19. de Lima, E.P.; Tanaka, M.; Lamas, C.B.; Quesada, K.; Detregiachi, C.R.P.; Araujo, A.C.; Guiguer, E.L.; Catharin, V.; de Castro, M.V.M.; Junior, E.B.; et al. Vascular Impairment, Muscle Atrophy, and Cognitive Decline: Critical Age-Related Conditions.Biomedicines 2024, 12, 2096.
20. Nunes, Y.C.; Mendes, N.M.; Pereira de Lima, E.; Chehadi, A.C.; Lamas, C.B.; Haber, J.F.S.; Dos Santos Bueno, M.; Araujo, A.C.;Catharin, V.C.S.; Detregiachi, C.R.P.; et al. Curcumin: A Golden Approach to Healthy Aging: A Systematic Review of the Evidence. Nutrients 2024, 16, 2721.
21. Ramnauth, A.D.; Tippani, M.; Divecha, H.R.; Papariello, A.R.; Miller, R.A.; Nelson, E.D.; Thompson, J.R.; Pattie, E.A.; Kleinman, J.E.; Maynard, K.R.; 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.
22. Wu, Y.; Korobeynyk, V.I.; Zamboni, M.;Waern, F.; Cole, J.D.; Mundt, S.; Greter, M.; Frisen, J.; Llorens-Bobadilla, E.; Jessberger, S. Multimodal transcriptomics reveal neurogenic aging trajectories and age-related regional inflammation in the dentate gyrus. Nat. Neurosci. 2025, 28, 415–430.
23. Mathews, K.J.; Allen, K.M.; Boerrigter, D.; Ball, H.; Shannon Weickert, C.; Double, K.L. Evidence for reduced neurogenesis in theaging human hippocampus despite stable stem cell markers. Aging Cell 2017, 16, 1195–1199.
24. Bedrosian, T.A.; Houtman, J.; Eguiguren, J.S.; Ghassemzadeh, S.; Rund, N.; Novaresi, N.M.; Hu, L.; Parylak, S.L.; Denli, A.M.;Randolph-Moore, L.; et al. Lamin B1 decline underlies age-related loss of adult hippocampal neurogenesis. EMBO J. 2021, 40,e105819.
25. Ishijima, T.; Nakajima, K. Inflammatory cytokines TNFα, IL-1β, and IL-6 are induced in endotoxin- stimulated microglia through different signaling cascades. Sci. Prog. 2021, 104, 368504211054985.
26. Tanaka, M.; Battaglia, S. From Biomarkers to Behavior: Mapping the NeuroimmuneWeb of Pain, Mood, and Memory. Biomedicines 2025, 13, 2226.
27. Araki, T.; Ikegaya, Y.; Koyama, R. The effects of microglia-and astrocyte-derived factors on neurogenesis in health and disease. Eur. J. Neurosci. 2021, 54, 5880–5901.
28. Nelson, L.H.; Peketi, P.; Lenz, K.M. Microglia Regulate Cell Genesis in a Sex-dependent Manner in the Neonatal Hippocampus. Neuroscience 2021, 453, 237–255.
29. Mecca, C.; Giambanco, I.; Donato, R.; Arcuri, C. Microglia and Aging: The Role of the TREM2-DAP12 and CX3CL1-CX3CR1 Axes. Int. J. Mol. Sci. 2018, 19, 318.
30. Jurgens, H.A.; Johnson, R.W. Dysregulated neuronal-microglial cross-talk during aging, stress and inflammation. Exp. Neurol. 2012, 233, 40–48.
31. Zhang, J.; He, H.; Qiao, Y.; Zhou, T.; He, H.; Yi, S.; Zhang, L.; Mo, L.; Li, Y.; Jiang, W.; et al. Priming of microglia with IFN-γ impairs adult hippocampal neurogenesis and leads to depression-like behaviors and cognitive defects. Glia 2020, 68, 2674–2692.
32. Ekdahl, C.T. Microglial activation—Tuning and pruning adult neurogenesis. Front. Pharmacol. 2012, 3, 41.
33. Fruholz, I.; Meyer-Luehmann, M. The intricate interplay between microglia and adult neurogenesis in Alzheimer's disease. Front.Cell Neurosci. 2024, 18, 1456253.
34. Al-Onaizi, M.; Al-Khalifah, A.; Qasem, D.; ElAli, A. Role of Microglia in Modulating Adult Neurogenesis in Health and Neurodegeneration. Int. J. Mol. Sci. 2020, 21, 6875.
35. Gao, C.; Jiang, J.; Tan, Y.; Chen, S. Microglia in neurodegenerative diseases: Mechanism and potential therapeutic targets. SignalTransduct. Target. Ther. 2023, 8, 359.
36. Sanchez-Molina, P.; Almolda, B.; Gimenez-Llort, L.; Gonzalez, B.; Castellano, B. Chronic IL-10 overproduction disrupts microglianeuron dialogue similar to aging, resulting in impaired hippocampal neurogenesis and spatial memory. Brain Behav. Immun.2022, 101, 231–245.
37. De Lucia, C.; Rinchon, A.; Olmos-Alonso, A.; Riecken, K.; Fehse, B.; Boche, D.; Perry, V.H.; Gomez-Nicola, D. Microglia regulate ippocampal neurogenesis during chronic neurodegeneration. Brain Behav. Immun. 2016, 55, 179–190.
38. Dominguez-Rivas, E.; Avila-Munoz, E.; Schwarzacher, S.W.; Zepeda, A. Adult hippocampal neurogenesis in the context oflipopolysaccharide-induced neuroinflammation: A molecular cellular and behavioral review. Brain Behav. Immun. 2021, 97,286–302.
39. Chesnokova, V.; Pechnick, R.N.; Wawrowsky, K. Chronic peripheral inflammation, hippocampal neurogenesis, and behavior.Brain Behav. Immun. 2016, 58, 1–8.
40. Rusznak, K.; Horvath A, I.; Pohli-Toth, K.; Futacsi, A.; Kemeny, A.; Kiss, G.; Helyes, Z.; Czeh, B. Experimental Arthritis InhibitsAdult Hippocampal Neurogenesis in Mice. Cells 2022, 11, 791.
41. Zonis, S.; Pechnick, R.N.; Ljubimov, V.A.; Mahgerefteh, M.; Wawrowsky, K.; Michelsen, K.S.; Chesnokova, V. Chronic intestinalinflammation alters hippocampal neurogenesis. J. Neuroinflamm. 2015, 12, 65.
42. Liu, Q.; Zhang, J.; Xiao, C.; Su, D.; Li, L.; Yang, C.; Zhao, Z.; Jiang, W.; You, Z.; Zhou, T. Akebia saponin D protects hippocampalneurogenesis from microglia-mediated inflammation and ameliorates depressive-like behaviors and cognitive impairment inmice through the PI3K-Akt pathway. Front. Pharmacol. 2022, 13, 927419.
43. Ekdahl, C.T.; Claasen, J.H.; Bonde, S.; Kokaia, Z.; Lindvall, O. Inflammation is detrimental for neurogenesis in adult brain. Proc.Natl. Acad. Sci. USA 2003, 100, 13632–13637.
44. Golia, M.T.; Poggini, S.; Alboni, S.; Garofalo, S.; Ciano Albanese, N.; Viglione, A.; Ajmone-Cat, M.A.; St-Pierre, A.; Brunello, N.;Limatola, C.; et al. Interplay between inflammation and neural plasticity: Both immune activation and suppression impair LTPand BDNF expression. Brain Behav. Immun. 2019, 81, 484–494.
45. Miguel-Hidalgo, J.J.; Pang, Y. Role of neuroinflammation in the establishment of the neurogenic microenvironment in braindiseases. Curr. Tissue Microenviron. Rep. 2021, 2, 17–28.
46. Li, X.; Li, Y.; Jin, Y.; Zhang, Y.;Wu, J.; Xu, Z.; Huang, Y.; Cai,

L.; Gao, S.; Liu, T.; et al. Transcriptional and epigenetic decoding ofthe microglial aging process. Nat. Aging 2023, 3, 1288–1311.
47. Wang, W.; Wang, M.; Yang, M.; Zeng, B.; Qiu, W.; Ma, Q.; Jing, X.; Zhang, Q.; Wang, B.; Yin, C.; et al. Transcriptome dynamics ofhippocampal neurogenesis in macaques across the lifespan and aged humans. Cell Res. 2022, 32, 729–743.
48. Grabert, K.; Michoel, T.; Karavolos, M.H.; Clohisey, S.; Baillie, J.K.; Stevens, M.P.; Freeman, T.C.; Summers, K.M.; McColl,B.W. Microglial brain region-dependent diversity and selective regional sensitivities to aging. Nat. Neurosci. 2016, 19, 504–516.
49. Tan, Y.L.; Yuan, Y.; Tian, L. Microglial regional heterogeneity and its role in the brain. Mol. Psychiatry 2020, 25, 351–367.
50. Yu, H.; Chang, Q.; Sun, T.; He, X.;Wen, L.; An, J.; Feng, J.; Zhao, Y. Metabolic reprogramming and polarization of microglia inParkinson's disease: Role of inflammasome and iron. Ageing Res. Rev. 2023, 90, 102032.
51. Petralla, S.; De Chirico, F.; Miti, A.; Tartagni, O.; Massenzio, F.; Poeta, E.; Virgili, M.; Zuccheri, G.; Monti, B. Epigenetics andCommunication Mechanisms in Microglia Activation with a View on Technological Approaches. Biomolecules 2021, 11, 306.
52. Zhang, X.; Wang, R.; Chen, H.; Jin, C.; Jin, Z.; Lu, J.; Xu, L.; Lu, Y.; Zhang, J.; Shi, L. Aged microglia promote peripheral T cellinfiltration by reprogramming the microenvironment of neurogenic niches. Immun. Ageing 2022, 19, 34.
53. Bisht, K.; Okojie, K.A.; Sharma, K.; Lentferink, D.H.; Sun, Y.Y.; Chen, H.R.; Uweru, J.O.; Amancherla, S.; Calcuttawala, Z.;Campos-Salazar, A.B.; et al. Capillary-associated microglia regulate vascular structure and function through PANX1-P2RY12 coupling in mice. Nat. Commun. 2021, 12, 5289.
54. Brubaker, D.K.; Lauffenburger, D.A. Translating preclinical models to humans. Science 2020, 367, 742–743.
55. Gault, N.; Szele, F.G. Immunohistochemical evidence for adult human neurogenesis in health and disease. WIREs Mech. Dis.2021, 13, e1526.
56. Cutler, R.R.; Kokovay, E. Rejuvenating subventricular zone neurogenesis in the aging brain. Curr. Opin. Pharmacol. 2020, 50, 1–8.
57. Ji, S.; Xiong, M.; Chen, H.; Liu, Y.; Zhou, L.; Hong, Y.; Wang, M.; Wang, C.; Fu, X.; Sun, X. Cellular rejuvenation: Molecularmechanisms and potential therapeutic interventions for diseases. Signal Transduct. Target. Ther. 2023, 8, 116.
58. Gillotin, S.; Sahni, V.; Lepko, T.; Hanspal, M.A.; Swartz, J.E.; Alexopoulou, Z.; Marshall, F.H. Targeting impaired adult hippocampalneurogenesis in ageing by leveraging intrinsic mechanisms regulating Neural Stem Cell activity. Ageing Res. Rev. 2021, 71, 101447.
59. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. An update on role of mitochondrial transport in etiopathogenesis & management of various CNS diseases, neurodegenerative diseases, immunometabolic diseases, cancer, viral infections inclusive of COVID 19 disease-a systematic review. J Diab Metab Disorder Control. 2021;8(3):91–103. DOI: 10.15406/jdmdc.2021.08.00228.
60. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. An Update on Role of Bile Acids in Neurological Functions and Neurodegenerative Diseases: A Narrative Review. J ClinBiomed Invest. 2023;3(2): 22-39. doi: 10.52916/jcbi224026
61. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. An update on role of mitochondrial transport in etiopathogenesis & management of various CNS diseases, neurodegenerative diseases, immunometabolic diseases, cancer, viral infections inclusive of COVID 19 disease-a systematic review. J Diab Metab Disorder Control. 2021;8(3):91–103. DOI: 10.15406/jdmdc.2021.08.00228.
62. Kulvinder Kochar Kaur,Allahbadia GN,Singh M."Iridoids. Some Monotepenes and Other Natural Products for Development of Potential Therapies inAlzheimer's Disease-A Review". Nutrition and Food Toxicology 3.5 (2019): 741-756.
63. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. A Comprehensive Update on the Etiopathogenesis of Amyotrophic Lateral Sclerosis with Specific Emphasis on Gut Microbiota (GM), Enteric Nervous System (ENS) and Associated Crosstalk of Astrocytes, GM, Muscle with Mitochondrial Melatonergic Pathway-A Narrative Review. Int J Neurobiol 5(2): 158 DOI: https://doi.org/10.36266/IJN/158
64. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. .An update on the manner Adenylyl cyclases (ACs) might be the therapeutic targets regarding neurodegenerative diseases(NDD) treatment:A review'' J. of Adv Clin Neu Res2025.; 1(2), 01-29. WMJ/JACNR-110DOI: doi.org/10.63721/25JACNR0110
65. Kulvinder Kochar Kaur'Association of acetyl-CoA Phenotypes of cholinergic neurons' with ATP-citrate lyase: practical application-A Mini Review'' J. of Adv Clin Neu Res 2(2), 01-17. WMJ/JACNR-122.
66. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Update on Etiopathogenesis of Type 1 Diabetes (T1D): Emphasis on Part of Crosstalk of Gut Microbiome, Pancreatic Cells & Bystander Activation of Memory CD8+T Cells with Mitochondrial Melatonergic Pathway: Treatment Repercussions - A Narrative Review Universal Library of Medical and Health Sciences2024;1(1):41-64.
67. Kulvinder Kochar Kaur,Allahbadia GN,Singh M.'Targeting Mechanistically interaction Amongst neuron-glia redox signalling subsequent to CNS damage/ neurodegenerative diseases(NDD) generation: specifically Astrocytic antioxidant mechanistic modes -A Review'' J of Adv Clin Neu Re2026; 2(1), 01-34. WMJ/JACNR-114DOI: doi.org/10.63721/26JACNR0114
68. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. The importance of Dysbiosis in Intestinal flora Subsequent to ischaemic Stroke: Implications in Therapeutic Management and Biomarkers for Prognosis-A Narrative Review, J. Clinical and Medical Research and Studies. 2023;2(1).
69. Kulvinder Kochar Kaur,Allahbadia GN,Singh

M. Impairment of Glymphatic Systemincluding Aquaporin-4 (AQP4): a newer perspective oftherapy of neurodegenerative diseases / Chronic traumaticencephalopathy Ischemic stroke & amp; Vascular dementia:A Review. American J Med Res Rev. 2026, 1(1), 01-12.

70. Kulvinder Kochar Kaur,Allahbadia GN,Singh M.Exciting hope for Professional Women marrying Late - manipulating NAD+ Metabolism -A-Bright Future Prospect-A narrative review'' Chronicles of Clinical Reviews and Case Reports, The Geek Chronicles, 1, 1-30
71. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. 'Are we any close to utilizing targeting SIRT signaling pathway for enhancing the oocyte quality in women with advanced maternalage :bringing from bench to bedside : A Narrative Review'' 72.Kulvinder Kochar Kaur,Allahbadia GN,Singh M .Are we any Close to Utilizing Targeting SIRT Signaling Pathway for Enhancingthe Oocyte Quality in Women with Advanced Maternal age: Bringing from Bench to Bedside: A Narrative Review. J Gynecol 2023, 8(2): 000257. DOI: 10.23880/oajg-16000257.
72. Kulvinder Kochar Kaur,Allahbadia GN,Singh M . Leydig-like cells synthesis: strategies, evaluationof propertiesand hurdles encountered-Anarrative review'' Accepted for Publication in Perceptions in Reproductive Medicine 2025
73. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. An Update on the Innovative Part of NLRP3 Inflammasome Regarding Newer Strategies for Treatmentof Reproductive Conditions Possessing Greater Risk: A Systematic Review J Gynecol2022;7(3):1-13. DOI: 10.23880/oajg-16000237. Niklison-Chirou, M.V.; Agostini, M.; Amelio, I.; Melino, G. Regulation of Adult Neurogenesis in Mammalian Brain. Int. J. Mol. Sci. 2020, 21, 4869.
74. Abbott, L.C.; Nigussie, F. Adult neurogenesis in the mammalian dentate gyrus. Anat. Histol. Embryol. 2020, 49, 3–16.
75. Nishiyama, R.; Nakagomi, T.; Nakano-Doi, A.; Kuramoto, Y.; Tsuji, M.; Yoshimura, S. Neonatal Brains Exhibit Higher Neural Reparative Activities than Adult Brains in a Mouse Model of Ischemic Stroke. Cells 2024, 13, 519.
76. Merkle, F.T.; Tramontin, A.D.; Garcia-Verdugo, J.M.; Alvarez-Buylla, A. Radial glia give rise to adult neural stem cells in the subventricular zone. Proc. Natl. Acad. Sci. USA 2004, 101, 17528–17532.
77. Zaritsky, R.; Kumari, E.; Velloso, F.J.; Lemenze, A.; Husain, S.; Levison, S.W. Transcriptional Profiling Defines Unique Subtypes of Transit Amplifying Neural ProgenitorsWithin the Neonatal Mouse Subventricular Zone. Biomolecules 2025, 15, 1438.
78. Nicaise, A.M.;Willis, C.M.; Crocker, S.J.; Pluchino, S. Stem Cells of the Aging Brain. Front. Aging Neurosci. 2020, 12, 247.
79. Peng, H.; Whitney, N.; Wu, Y.; Tian, C.; Dou, H.; Zhou, Y.; Zheng, J. HIV-1-infected and/or immune-activated macrophagesecreted TNF-alpha affects human fetal cortical neural progenitor cell proliferation and differentiation. Glia 2008, 56, 903–916.
80. Vidal, P.M.; Lemmens, E.; Dooley, D.; Hendrix, S. The role of "anti-inflammatory" cytokines in axon regeneration. Cytokine Growth Factor. Rev. 2013, 24, 1–12.
81. Liang, Z.; Jin, N.; Guo,W. Neural stem cell heterogeneity in adult hippocampus. Cell Regen. 2025, 14, 6.
82. Calabrese, V.; Santoro, A.; Monti, D.; Crupi, R.; Di Paola, R.; Latteri, S.; Cuzzocrea, S.; Zappia, M.; Giordano, J.; Calabrese, E.J.; et al.Aging and Parkinson's Disease: Inflammaging, neuroinflammation and biological remodeling as key factors in pathogenesis. FreeRadic. Biol. Med. 2018, 115, 80–91.
83. Tanaka, M.; Vecsei, L. From Microbial Switches to Metabolic Sensors: Rewiring the Gut-Brain Kynurenine Circuit. Biomedicines2025, 13, 2020.
84. Barbalho, S.M.; Leme Boaro, B.; da Silva Camarinha Oliveira, J.; Patoˇcka, J.; Barbalho Lamas, C.; Tanaka, M.; Laurindo, L.F.Molecular Mechanisms Underlying Neuroinflammation Intervention with Medicinal Plants: A Critical and Narrative Review ofthe Current Literature. Pharmaceuticals 2025, 18, 133.
85. Duan, X.; Kang, E.; Liu, C.Y.; Ming, G.L.; Song, H. Development of neural stem cell in the adult brain. Curr. Opin. Neurobiol. 2008,18, 108–115. [CrossRef] [PubMed]
86. Obernier, K.; Alvarez-Buylla, A. Neural stem cells: Origin, heterogeneity and regulation in the adult mammalian brain. Development2019, 146, dev156059. [CrossRef]
87. 88. Kempermann, G.; Song, H.; Gage, F.H. Neurogenesis in the Adult Hippocampus. Cold Spring Harb. Perspect. Biol. 2015, 7, a018812.
88. Cope, E.C.; Gould, E. Adult Neurogenesis, Glia, and the Extracellular Matrix. Cell Stem Cell 2019, 24, 690–705. [CrossRef] [PubMed]
89. Sakamoto, M.; Kageyama, R.; Imayoshi, I. The functional significance of newly born neurons integrated into olfactory bulb circuits. Front. Neurosci. 2014, 8, 121. [CrossRef]
90. Deshpande, A.; Bergami, M.; Ghanem, A.; Conzelmann, K.K.; Lepier, A.; Gotz, M.; Berninger, B. Retrograde monosynaptic tracing reveals the temporal evolution of inputs onto new neurons in the adult dentate gyrus and olfactory bulb. Proc. Natl. Acad. Sci. USA 2013, 110, E1152–E1161. [CrossRef] Faigle, R.; Song, H. Signaling mechanisms regulating adult neural stem cells and neurogenesis. Biochim. Biophys. Acta 2013, 1830, 2435–2448. [CrossRef] [PubMed]
91. Shi, J.; Wang, Z.; Wang, Z.; Shao, G.; Li, X. Epigenetic regulation in adult neural stem cells. Front. Cell Dev. Biol. 2024, 12, 1331074. [CrossRef]
92. Horgusluoglu, E.; Nudelman, K.; Nho, K.; Saykin, A.J. Adult neurogenesis and neurodegenerative diseases: A systems biology perspective. Am. J. Med. Genet. B Neuropsychiatr. Genet. 2017, 174, 93–112. [CrossRef] [PubMed]
93. Batiz, L.F.; Castro, M.A.; Burgos, P.V.; Velasquez, Z.D.; Munoz, R.I.; Lafourcade, C.A.; Troncoso-Escudero, P.; Wyneken, U. Exosomes as Novel Regulators of Adult

Neurogenic Niches. Front. Cell Neurosci. 2015, 9, 501. [CrossRef]
94. Li, Y.; Guo,W. Neural Stem Cell Niche and Adult Neurogenesis. Neuroscientist 2021, 27, 235–245. [CrossRef] [PubMed]
95. Quaresima, S.; Istiaq, A.; Jono, H.; Cacci, E.; Ohta, K.; Lupo, G. Assessing the Role of Ependymal and Vascular Cells as Sources of Extracellular Cues Regulating the Mouse Ventricular-Subventricular Zone Neurogenic Niche. Front. Cell Dev. Biol. 2022, 10, 845567. [CrossRef] [PubMed]
96. Kuhn, H.G.; Dickinson-Anson, H.; Gage, F.H. Neurogenesis in the dentate gyrus of the adult rat: Age-related decrease of neuronal progenitor proliferation. J. Neurosci. 1996, 16, 2027–2033. [CrossRef] [PubMed]
97. Lee, S.W.; Clemenson, G.D.; Gage, F.H. New neurons in an aged brain. Behav. Brain Res. 2012, 227, 497–507. [CrossRef]
98. Bin Imtiaz, M.K.; Jaeger, B.N.; Bottes, S.; Machado, R.A.C.; Vidmar, M.; Moore, D.L.; Jessberger, S. Declining lamin B1 expression mediates age-dependent decreases of hippocampal stem cell activity. Cell Stem Cell 2021, 28, 967–977.e968. [CrossRef]
99. Bast, L.; Calzolari, F.; Strasser, M.K.; Hasenauer, J.; Theis, F.J.; Ninkovic, J.; Marr, C. Increasing Neural Stem Cell Division Asymmetry and Quiescence Are Predicted to Contribute to the Age-Related Decline in Neurogenesis. Cell Rep. 2018, 25, 3231–3240.e3238. [CrossRef]
100. Pineda, J.R.; Daynac, M.; Chicheportiche, A.; Cebrian-Silla, A.; Sii Felice, K.; Garcia-Verdugo, J.M.; Boussin, F.D.; Mouthon, M.A. Vascular-derived TGF-β increases in the stem cell niche and perturbs neurogenesis during aging and following irradiation in the adult mouse brain. EMBO Mol. Med. 2013, 5, 548–562. [CrossRef]
101. Buckwalter, M.S.; Yamane, M.; Coleman, B.S.; Ormerod, B.K.; Chin, J.T.; Palmer, T.; Wyss-Coray, T. Chronically increased transforming growth factor-beta1 strongly inhibits hippocampal neurogenesis in aged mice. Am. J. Pathol. 2006, 169, 154–164. [CrossRef]
102. DeCarolis, N.A.; Kirby, E.D.; Wyss-Coray, T.; Palmer, T.D. The Role of the Microenvironmental Niche in Declining Stem-Cell Functions Associated with Biological Aging. Cold Spring Harb. Perspect. Med. 2015, 5, a025874. [CrossRef] [PubMed]
103. Tanaka, M.; Vecsei, L. A Decade of Dedication: Pioneering Perspectives on Neurological Diseases and Mental Illnesses. Biomedicines 2024, 12, 1083. [CrossRef]
104. Jimenez Peinado, P.; Urbach, A. From Youthful Vigor to Aging Decline: Unravelling the Intrinsic and Extrinsic Determinants of Hippocampal Neural Stem Cell Aging. Cells 2023, 12, 2086. [CrossRef] [PubMed]
105. Moreno-Jimenez, E.P.; Flor-Garcia, M.; Terreros-Roncal, J.; Rabano, A.; Cafini, F.; Pallas-Bazarra, N.; Avila, J.; Llorens-Martin, M. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. Nat. Med. 2019, 25, 554–560. [CrossRef] [PubMed]
106. Knoth, R.; Singec, I.; Ditter, M.; Pantazis, G.; Capetian, P.; Meyer, R.P.; Horvat, V.; Volk, B.; Kempermann, G. Murine features of neurogenesis in the human hippocampus across the lifespan from 0 to 100 years. PLoS ONE 2010, 5, e8809. [CrossRef]
107. Flor-Garcia, M.; Terreros-Roncal, J.; Moreno-Jimenez, E.P.; Avila, J.; Rabano, A.; Llorens-Martin, M. Unraveling human adult hippocampal neurogenesis. Nat. Protoc. 2020, 15, 668–693. [CrossRef]
108. Terreros-Roncal, J.; Flor-Garcia, M.; Moreno-Jimenez, E.P.; Rodriguez-Moreno, C.B.; Marquez-Valadez, B.; Gallardo-Caballero, M.; Rabano, A.; Llorens-Martin, M. Methods to study adult hippocampal neurogenesis in humans and across the phylogeny.Hippocampus 2023, 33, 271–306. [CrossRef] Seki, T. Understanding the Real State of Human Adult Hippocampal Neurogenesis From Studies of Rodents and Non-human Primates. Front. Neurosci. 2020, 14, 839. [CrossRef]
109. Gulen, M.F.; Samson, N.; Keller, A.; Schwabenland, M.; Liu, C.; Gluck, S.; Thacker, V.V.; Favre, L.; Mangeat, B.; Kroese, L.J.; et al. cGAS-STING drives ageing-related inflammation and neurodegeneration. Nature 2023, 620, 374–380. [CrossRef]
110. Costa, J.; Martins, S.; Ferreira, P.A.; Cardoso, A.M.S.; Guedes, J.R.; Peca, J.; Cardoso, A.L. The old guard: Age-related changes in microglia and their consequences. Mech. Ageing Dev. 2021, 197, 111512. [CrossRef] [PubMed]
111. Koellhoffer, E.C.; McCullough, L.D.; Ritzel, R.M. Old Maids: Aging and Its Impact on Microglia Function. Int. J. Mol. Sci. 2017, 18,769. [CrossRef]
112. Ana, B. Aged-Related Changes in Microglia and Neurodegenerative Diseases: Exploring the Connection. Biomedicines 2024, 12,1737. [CrossRef]
113. Škandik, M.; Friess, L.; Vazquez-Cabrera, G.; Keane, L.; Grabert, K.; Cruz De Los Santos, M.; Posada-Perez, M.; Baleviciute, A.;Cheray, M.; Joseph, B. Age-associated microglial transcriptome leads to diminished immunogenicity and dysregulation of MCT4and P2RY12/P2RY13 related functions. Cell Death Discov. 2025, 11, 16. [CrossRef] [PubMed]
114. Edler, M.K.; Mhatre-Winters, I.; Richardson, J.R. Microglia in Aging and Alzheimer's Disease: A Comparative Species Review.Cells 2021, 10, 1138. [CrossRef]
115. O'Neil, S.M.; Hans, E.E.; Jiang, S.; Wangler, L.M.; Godbout, J.P. Astrocyte immunosenescence and deficits in interleukin 10signaling in the aged brain disrupt the regulation of microglia following innate immune activation. Glia 2022, 70, 913–934. [CrossRef] [PubMed]
116. Tamatta, R.; Pai, V.; Jaiswal, C.; Singh, I.; Singh, A.K. Neuroinflammaging and the Immune Landscape: The Role of Autophagyand Senescence in Aging Brain. Biogerontology 2025, 26, 52. [CrossRef] [PubMed]
117. Lutshumba, J.; Nikolajczyk, B.S.; Bachstetter, A.D. Dysregulation of Systemic Immunity in Aging and Dementia. Front. CellNeurosci. 2021, 15, 652111. [CrossRef]
118. Escartin, C.; Galea, E.; Lakatos, A.; O'Callaghan, J.P.; Petzold, G.C.; Serrano-Pozo, A.; Steinhauser, C.; Volterra,

A.; Carmignoto, G.;Agarwal, A.; et al. Reactive astrocyte nomenclature, definitions, and future directions. Nat. Neurosci. 2021, 24, 312–325. [CrossRef][PubMed]
119. Patani,R.;Hardingham,G.E.;Liddelow,S.A.Functional roles of reactive astrocytes in neuroinflammation and neurodegeneration.Nat. Rev. Neurol. 2023, 19, 395–409. [CrossRef]
120. Jha, M.K.; Jo, M.; Kim, J.H.; Suk, K. Microglia-Astrocyte Crosstalk: An Intimate Molecular Conversation. Neuroscientist 2019, 25, 227–240. [CrossRef]
121. Li, K.; Li, J.; Zheng, J.; Qin, S. Reactive Astrocytes in Neurodegenerative Diseases. Aging Dis. 2019, 10, 664–675. [CrossRef]
122. Sobral, A.F.; Costa, I.; Teixeira, V.; Silva, R.; Barbosa, D.J. Molecular Motors in Blood-Brain Barrier Maintenance by Astrocytes.Brain Sci. 2025, 15, 279. [CrossRef]
123. Mohammad, Z.B.; Yudin, S.C.Y.; Goldberg, B.J.; Serra, K.L.; Klegeris, A. Exploring neuroglial signaling: Diversity of moleculesimplicated in microglia-to-astrocyte neuroimmune communication. Rev. Neurosci. 2025, 36, 91–117. [CrossRef]
124. Wang, S.; Pan, Y.; Zhang, C.; Zhao, Y.; Wang, H.; Ma, H.; Sun, J.; Zhang, S.; Yao, J.; Xie, D.; et al. Transcriptome Analysis RevealsDynamic Microglial-Induced A1 Astrocyte Reactivity via C3/C3aR/NF-κB Signaling After Ischemic Stroke. Mol. Neurobiol. 2024, 61, 10246–10270. [CrossRef]
125. Bhusal, A.; Afridi, R.; Lee, W.H.; Suk, K. Bidirectional Communication Between Microglia and Astrocytes in Neuroinflammation. Curr. Neuropharmacol. 2023, 21, 2020–2029. [CrossRef]
126. Norden, D.M.; Godbout, J.P. Review: Microglia of the aged brain: Primed to be activated and resistant to regulation. Neuropathol. Appl. Neurobiol. 2013, 39, 19–34. [CrossRef]
127. Elmore, M.R.P.; Hohsfield, L.A.; Kramar, E.A.; Soreq, L.; Lee, R.J.; Pham, S.T.; Najafi, A.R.; Spangenberg, E.E.; Wood, M.A.; West,B.L.; et al. Replacement of microglia in the aged brain reverses cognitive, synaptic, and neuronal deficits in mice. Aging Cell 2018, 17, e12832. [CrossRef] [PubMed]
128. Niraula, A.; Sheridan, J.F.; Godbout, J.P. Microglia Priming with Aging and Stress. Neuropsychopharmacology 2017, 42, 318–333. [CrossRef] [PubMed]
129. Norden, D.M.; Muccigrosso, M.M.; Godbout, J.P. Microglial priming and enhanced reactivity to secondary insult in aging, andtraumatic CNS injury, and neurodegenerative disease. Neuropharmacology 2015, 96, 29–41. [CrossRef]
130. Neher, J.J.; Cunningham, C. Priming Microglia for Innate Immune Memory in the Brain. Trends Immunol. 2019, 40, 358–374. [CrossRef]
131. Hoeijmakers, L.; Heinen, Y.; van Dam, A.M.; Lucassen, P.J.; Korosi, A. Microglial Priming and Alzheimer's Disease: A PossibleRole for (Early) Immune Challenges and Epigenetics? Front. Hum. Neurosci. 2016, 10, 398. [CrossRef]
132. O'Neil, S.M.;Witcher, K.G.; McKim, D.B.; Godbout, J.P. Forced turnover of aged microglia induces an intermediate phenotypebut does not rebalance CNS environmental cues driving priming to immune challenge. Acta Neuropathol. Commun. 2018, 6, 129. [CrossRef]
133. Wahl, D.; Risen, S.J.; Osburn, S.C.; Emge, T.; Sharma, S.; Gilberto, V.S.; Chatterjee, A.; Nagpal, P.; Moreno, J.A.; LaRocca, T.J.Nanoligomers targeting NF-κB and NLRP3 reduce neuroinflammation and improve cognitive function with aging and tauopathy. J. Neuroinflamm. 2024, 21, 182. [CrossRef] [PubMed]
134. Li, Y.; Xia, Y.; Yin, S.;Wan, F.; Hu, J.; Kou, L.; Sun, Y.;Wu, J.; Zhou, Q.; Huang, J.; et al. Targeting Microglial α-Synuclein/TLRs/NFkappaB/NLRP3 Inflammasome Axis in Parkinson's Disease. Front. Immunol. 2021, 12, 719807. [CrossRef]
135. Lei, L.Y.;Wang, R.C.; Pan, Y.L.; Yue, Z.G.; Zhou, R.; Xie, P.; Tang, Z.S. Mangiferin inhibited neuroinflammation through regulatingmicroglial polarization and suppressing NF-κB, NLRP3 pathway. Chin. J. Nat. Med. 2021, 19, 112–119. [CrossRef]
136. Wang, T.; Liu, Y.; Lu, Y.; Chi, L. NTN-1 attenuates amyloid-β-mediated microglial neuroinflammation and memory impairment via the NF-κB pathway and NLRP3 inflammasome in a rat model of Alzheimer's disease. Front. Aging Neurosci. 2025, 17, 1516399. [CrossRef] [PubMed]
137. Fornari Laurindo, L.; Aparecido Dias, J.; Cressoni Araujo, A.; Torres Pomini, K.; Machado Galhardi, C.; Rucco Penteado Detregiachi,C.; Santos de Argollo Haber, L.; Donizeti Roque, D.; Dib Bechara, M.; Vialogo Marques de Castro, M.; et al. Immunologicaldimensions of neuroinflammation and microglial activation: Exploring innovative immunomodulatory approaches to mitigateneuroinflammatory progression. Front. Immunol. 2023, 14, 1305933. [CrossRef]
138. Borsini, A.; Zunszain, P.A.; Thuret, S.; Pariante, C.M. The role of inflammatory cytokines as key modulators of neurogenesis.Trends Neurosci. 2015, 38, 145–157. [CrossRef]
139. Kong, X.; Gong, Z.; Zhang, L.; Sun, X.; Ou, Z.; Xu, B.; Huang, J.; Long, D.; He, X.; Lin, X.; et al. JAK2/STAT3 signaling mediatesIL-6-inhibited neurogenesis of neural stem cells through DNA demethylation/methylation. Brain Behav. Immun. 2019, 79, 159–173. [CrossRef] [PubMed]
140. Salminen, A.; Ojala, J.; Kaarniranta, K.; Kauppinen, A. Mitochondrial dysfunction and oxidative stress activate inflammasomes:Impact on the aging process and age-related diseases. Cell Mol. Life Sci. 2012, 69, 2999–3013. [CrossRef] [PubMed]
141. Tanaka, M.; Szabo, A.; Vecsei, L. Redefining Roles: A Paradigm Shift in Tryptophan-Kynurenine Metabolism for InnovativeClinical Applications. Int. J. Mol. Sci. 2024, 25, 12767. [CrossRef]
142. 145. Juhasz, L.; Spisak, K.; Szolnoki, B.Z.; Naszai, A.; Szabo, A.; Rutai, A.; Tallosy, S.P.; Szabo, A.; Toldi, J.; Tanaka, M.; et al. ThePower Struggle: Kynurenine Pathway Enzyme Knockouts and Brain Mitochondrial Respiration.

J. Neurochem. 2025, 169, e70075. [CrossRef]
143. Sarkar, S.; Malovic, E.; Harishchandra, D.S.; Ghaisas, S.; Panicker, N.; Charli, A.; Palanisamy, B.N.; Rokad, D.; Jin, H.; Anantharam,V.; et al. Mitochondrial impairment in microglia amplifies NLRP3 inflammasome proinflammatory signaling in cell culture and animal models of Parkinson's disease. NPJ Park. Dis. 2017, 3, 30. [CrossRef]
144. Hansen, C.E.; Vacondio, D.; van der Molen, L.; Juttner, A.A.; Fung,W.K.; Karsten, M.; van Het Hof, B.; Fontijn, R.D.; Kooij, G.;Witte, M.E.; et al. Endothelial-Ercc1 DNA repair deficiency provokes blood-brain barrier dysfunction. Cell Death Dis. 2025, 16, 1. [CrossRef]
145. Dulken, B.W.; Buckley, M.T.; Navarro Negredo, P.; Saligrama, N.; Cayrol, R.; Leeman, D.S.; George, B.M.; Boutet, S.C.; Hebestreit,K.; Pluvinage, J.V.; et al. Single-cell analysis reveals T cell infiltration in old neurogenic niches. Nature 2019, 571, 205–210. [CrossRef]
146. Moreno-Valladares, M.; Moreno-Cugnon, L.; Silva, T.M.; Garces, J.P.; Saenz-Antonanzas, A.; Alvarez-Satta, M.; Matheu, A. CD8(+)T cells are increased in the subventricular zone with physiological and pathological aging. Aging Cell 2020, 19, e13198. [CrossRef]
147. Solano Fonseca, R.; Mahesula, S.; Apple, D.M.; Raghunathan, R.; Dugan, A.; Cardona, A.; O'Connor, J.; Kokovay, E. NeurogenicNiche Microglia Undergo Positional Remodeling and Progressive Activation Contributing to Age-Associated Reductions in Neurogenesis. Stem Cells Dev. 2016, 25, 542–555. [CrossRef]
148. Fonken, L.K.; Gaudet, A.D. Neuroimmunology of healthy brain aging. Curr. Opin. Neurobiol. 2022, 77, 102649. [CrossRef]
149. Chintamen, S.; Imessadouene, F.; Kernie, S.G. Immune Regulation of Adult Neurogenic Niches in Health and Disease. Front. CellNeurosci. 2020, 14, 571071. [CrossRef]
150. Diaz-Aparicio, I.; Paris, I.; Sierra-Torre, V.; Plaza-Zabala, A.; Rodriguez-Iglesias, N.; Marquez-Ropero, M.; Beccari, S.; Huguet, P.;Abiega, O.; Alberdi, E.; et al. Microglia Actively Remodel Adult Hippocampal Neurogenesis through the Phagocytosis Secretome.J. Neurosci. 2020, 40, 1453–1482. [CrossRef] [PubMed]
151. Sierra, A.; Encinas, J.M.; Deudero, J.J.; Chancey, J.H.; Enikolopov, G.; Overstreet-Wadiche, L.S.; Tsirka, S.E.; Maletic-Savatic,M. Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. Cell Stem Cell 2010, 7, 483–495. [CrossRef] [PubMed]
152. Kurematsu, C.; Sawada, M.; Ohmuraya, M.; Tanaka, M.; Kuboyama, K.; Ogino, T.; Matsumoto, M.; Oishi, H.; Inada, H.; Ishido,Y.; et al. Synaptic pruning of murine adult-born neurons by microglia depends on phosphatidylserine. J. Exp. Med. 2022, 219, e20202304. [CrossRef] [PubMed]
153. Jiang, X.; Yi, S.; Liu, Q.; Zhang, J. The secretome of microglia induced by IL-4 of IFN-γ differently regulate proliferation,differentiation and survival of adult neural stem/progenitor cell by targeting the PI3K-Akt pathway. Cytotechnology 2022, 74, 407–420. [CrossRef]
154. Matsui, T.K.; Mori, E. Microglia support neural stem cell maintenance and growth. Biochem. Biophys. Res. Commun. 2018, 503,1880–1884. [CrossRef] [PubMed]
155. Wlodarczyk, A.; Holtman, I.R.; Krueger, M.; Yogev, N.; Bruttger, J.; Khorooshi, R.; Benmamar-Badel, A.; de Boer-Bergsma, J.J.;Martin, N.A.; Karram, K.; et al. A novel microglial subset plays a key role in myelinogenesis in developing brain. Embo J 2017, 36,3292–3308. [CrossRef] [PubMed]
156. Mallard, C.; Tremblay, M.E.; Vexler, Z.S. Microglia and Neonatal Brain Injury. Neuroscience 2019, 405, 68–76. [CrossRef]
157. Harley, S.B.R.; Willis, E.F.; Shaikh, S.N.; Blackmore, D.G.; Sah, P.; Ruitenberg, M.J.; Bartlett, P.F.; Vukovic, J. Selective Ablation ofBDNF from Microglia Reveals Novel Roles in Self-Renewal and Hippocampal Neurogenesis. J. Neurosci. 2021, 41, 4172–4186. [CrossRef] [PubMed]
158. Xu, H.; Gelyana, E.; Rajsombath, M.; Yang, T.; Li, S.; Selkoe, D. Environmental Enrichment Potently Prevents Microglia-MediatedNeuroinflammation by Human Amyloid β-Protein Oligomers. J. Neurosci. 2016, 36, 9041–9056. [CrossRef]
159. Mee-Inta, O.; Zhao, Z.W.; Kuo, Y.M. Physical Exercise Inhibits Inflammation and Microglial Activation. Cells 2019, 8, 691. [CrossRef]
160. Choi, J.Y.; Kim, J.Y.; Kim, J.Y.; Park, J.; Lee, W.T.; Lee, J.E. M2 Phenotype Microglia-derived Cytokine Stimulates Proliferation andNeuronal Differentiation of Endogenous Stem Cells in Ischemic Brain. Exp. Neurobiol. 2017, 26, 33–41. [CrossRef]
161. Orihuela, R.; McPherson, C.A.; Harry, G.J. Microglial M1/M2 polarization and metabolic states. Br. J. Pharmacol. 2016, 173, 649–665. [CrossRef]
162. Vay, S.U.; Flitsch, L.J.; Rabenstein, M.; Rogall, R.; Blaschke, S.; Kleinhaus, J.; Reinert, N.; Bach, A.; Fink, G.R.; Schroeter, M.;et al. The plasticity of primary microglia and their multifaceted effects on endogenous neural stem cells in vitro and in vivo. J.Neuroinflamm. 2018, 15, 226. [CrossRef]
163. Carrier, M.; Šimonˇciˇcova, E.; St-Pierre, M.K.; McKee, C.; Tremblay, M. Psychological Stress as a Risk Factor for AcceleratedCellular Aging and Cognitive Decline: The Involvement of Microglia-Neuron Crosstalk. Front. Mol. Neurosci. 2021, 14, 749737. [CrossRef]
164. Afridi, R.; Lee, W.H.; Suk, K. Microglia Gone Awry: Linking Immunometabolism to Neurodegeneration. Front. Cell Neurosci.2020, 14, 246. [CrossRef]
165. Pawelec, P.; Ziemka-Nalecz, M.; Sypecka, J.; Zalewska, T. The Impact of the CX3CL1/CX3CR1 Axis in Neurological Disorders.Cells 2020, 9, 2277. [CrossRef] [PubMed]
166. Vukovic, J.; Colditz, M.J.; Blackmore, D.G.; Ruitenberg, M.J.; Bartlett, P.F. Microglia modulate hippocampal neural precursoractivity in response to exercise and aging. J. Neurosci. 2012, 32, 6435–6443. [CrossRef]
167. Bolos, M.; Perea, J.R.; Terreros-Roncal, J.; Pallas-Bazarra, N.; Jurado-Arjona, J.; Avila, J.; Llorens-Martin, M. Absence of microglialCX3CR1 impairs the synaptic

integration of adult-born hippocampal granule neurons. Brain Behav. Immun. 2018, 68, 76–89. [CrossRef]
168. Morton, M.C.; Neckles, V.N.; Seluzicki, C.M.; Holmberg, J.C.; Feliciano, D.M. Neonatal Subventricular Zone Neural Stem CellsRelease Extracellular Vesicles that Act as a Microglial Morphogen. Cell Rep. 2018, 23, 78–89. [CrossRef]
169. Chen, X.; Jiang, M.; Li, H.;Wang, Y.; Shen, H.; Li, X.; Zhang, Y.;Wu, J.; Yu, Z.; Chen, G. CX3CL1/CX3CR1 axis attenuates early brain injury via promoting the delivery of exosomal microRNA-124 from neuron to microglia after subarachnoid hemorrhage. J. Neuroinflamm. 2020, 17, 209. [CrossRef]
170. Qian, H.D.; Song, X.Y.; He, G.W.; Peng X.N.; Chen, Y.; Huang, P.; Zhang, J.; Lin, X.Y.; Gao, Q.; Zhu, S.M.; et al. Muller Glial-Derived Small Extracellular Vesicles Mitigate RGC Degeneration by Suppressing Microglial Activation via Cx3cl1-Cx3cr1Signaling. Adv. Healthc. Mater. 2025, 14, e2404306. [CrossRef]
171. Fritze, J.; Muralidharan, C.; Stamp, E.; Ahlenius, H. Microglia undergo disease-associated transcriptional activation and CX3C motif chemokine receptor 1 expression regulates neurogenesis in the aged brain. Dev. Neurobiol. 2024, 84, 128–141. [CrossRef]
172. Barko, K.; Shelton, M.; Xue, X.; Afriyie-Agyemang, Y.; Puig, S.; Freyberg, Z.; Tseng, G.C.; Logan, R.W.; Seney, M.L. Brain regionandsex-specific transcriptional profiles of microglia. Front. Psychiatry 2022, 13, 945548. [CrossRef]
173. Spencer, S.J.; Basri, B.; Sominsky, L.; Soch, A.; Ayala, M.T.; Reineck, P.; Gibson, B.C.; Barrientos, R.M. High-fat diet worsensthe impact of aging on microglial function and morphology in a region-specific manner. Neurobiol. Aging 2019, 74, 121–134. [CrossRef]
174. Ribeiro Xavier, A.L.; Kress, B.T.; Goldman, S.A.; Lacerda de Menezes, J.R.; Nedergaard, M. A Distinct Population of Microglia Supports Adult Neurogenesis in the Subventricular Zone. J. Neurosci. 2015, 35, 11848–11861. [CrossRef]
175. Smith, L.K.; White, C.W., 3rd; Villeda, S.A. The systemic environment: At the interface of aging and adult neurogenesis. CellTissue Res. 2018, 371, 105–113. [CrossRef]
176. Lana, D.; Magni, G.; Landucci, E.;Wenk, G.L.; Pellegrini-Giampietro, D.E.; Giovannini, M.G. Phenomic Microglia Diversity as aDruggable Target in the Hippocampus in Neurodegenerative Diseases. Int. J. Mol. Sci. 2023, 24, 13668. [CrossRef]
177. Sato, K. Effects of Microglia on Neurogenesis. Glia 2015, 63, 1394–1405. [CrossRef]
178. Chintamen, S.; Gaur, P.; Vo, N.; Bradshaw, E.M.; Menon, V.; Kernie, S.G. Distinct microglial transcriptomic signatures within thehippocampus. PLoS ONE 2024, 19, e0296280. [CrossRef]
179. McKee, C.G.; Hoffos, M.; Vecchiarelli, H.A.; Tremblay, M. Microglia: A pharmacological target for the treatment of age-relatedcognitive decline and Alzheimer's disease. Front. Pharmacol. 2023, 14, 1125982. [CrossRef]
180. McGroarty, J.; Salinas, S.; Evans, H.; Jimenez, B.; Tran, V.; Kadavakollu, S.; Vashist, A.; Atluri, V. Inflammasome-MediatedNeuroinflammation: A Key Driver in Alzheimer's Disease Pathogenesis. Biomolecules 2025, 15, 676. [CrossRef] [PubMed]
181. Xu,W.; Huang, Y.; Zhou, R. NLRP3 inflammasome in neuroinflammation and central nervous system diseases. Cell Mol. Immunol. 2025, 22, 341–355. [CrossRef] [PubMed]
182. Khilazheva, E.D.; Mosiagina, A.I.; Panina, Y.A.; Belozor, O.S.; Komleva, Y.K. Impact of NLRP3 Depletion on Aging-Related Metaflammation, Cognitive Function, and Social Behavior in Mice. Int. J. Mol. Sci. 2023, 24, 16580. [CrossRef]
183. Zhang, X.; Kracht, L.; Lerario, A.M.; Dubbelaar, M.L.; Brouwer, N.;Wesseling, E.M.; Boddeke, E.; Eggen, B.J.L.; Kooistra, S.M. Epigenetic regulation of innate immune memory in microglia. J. Neuroinflamm. 2022, 19, 111. [CrossRef] [PubMed]
184. Kamei, N.; Day, K.; Guo, W.; Haus, D.L.; Nguyen, H.X.; Scarfone, V.M.; Booher, K.; Jia, X.Y.; Cummings, B.J.; Anderson, A.J.Injured inflammatory environment overrides the TET2 shaped epigenetic landscape of pluripotent stem cell derived humanneural stem cells. Sci. Rep. 2024, 14, 25186. [CrossRef] [PubMed]
185. Itokawa, N.; Oshima, M.; Koide, S.; Takayama, N.; Kuribayashi, W.; Nakajima-Takagi, Y.; Aoyama, K.; Yamazaki, S.; Yamaguchi,K.; Furukawa, Y.; et al. Epigenetic traits inscribed in chromatin accessibility in aged hematopoietic stem cells. Nat. Commun. 2022,13, 2691. [CrossRef]
186. Zocher, S.; Toda, T. Epigenetic aging in adult neurogenesis. Hippocampus 2023, 33, 347–359. [CrossRef] [PubMed]
187. Prakash, R.; Waseem, A.; Siddiqui, A.J.; Naime, M.; Khan, M.A.; Robertson, A.A.; Boltze, J.; Raza, S.S. MCC950 mitigatesSIRT3-NLRP3-driven inflammation and rescues post-stroke neurogenesis. Biomed. Pharmacother. 2025, 183, 117861. [CrossRef]
188. Kodi, T.; Sankhe, R.; Gopinathan, A.; Nandakumar, K.; Kishore, A. New Insights on NLRP3 Inflammasome: Mechanisms ofActivation, Inhibition, and Epigenetic Regulation. J. Neuroimmune Pharmacol. 2024, 19, 7. [CrossRef] [PubMed]
189. Nakagomi, T. Unlocking the potential of regionally activated injury/ischemia-induced stem cells for neural regeneration. StemCells 2025, 43, sxaf015. [CrossRef] [PubMed]
190. Nakagomi, T.; Nakano-Doi, A.; Kubo, S.; Sawano, T.; Kuramoto, Y.; Yamahara, K.; Matsuyama, T.; Takagi, T.; Doe, N.; Yoshimura,S. Transplantation of Human Brain-Derived Ischemia-Induced Multipotent Stem Cells Ameliorates Neurological Dysfunction inMice After Stroke. Stem Cells Transl. Med. 2023, 12, 400–414. [CrossRef] [PubMed]
191. Holleman, J.; Daniilidou, M.; Kareholt, I.; Aspo, M.; Hagman, G.; Udeh-Momoh, C.T.; Spulber, G.; Kivipelto, M.; Solomon, A.;Matton, A.; et al. Diurnal cortisol, neuroinflammation, and neuroimaging visual rating scales in memory clinic patients. BrainBehav. Immun.

2024, 118, 499–509. [CrossRef]
192. Dutta, P.; Quax, R.; Crielaard, L.; Badiali, L.; Sloot, P.M.A. Inferring temporal dynamics from cross-sectional data using Langevindynamics. R. Soc. Open Sci. 2021, 8, 211374. [CrossRef]
193. Mroczek, M.; Desouky, A.; Sirry, W. Imaging Transcriptomics in Neurodegenerative Diseases. J. Neuroimaging 2021, 31, 244–250. [CrossRef]
194. Lee, N.; Choi, J.Y.; Ryu, Y.H. The development status of PET radiotracers for evaluating neuroinflammation. Nucl. Med. Mol.Imaging 2024, 58, 160–176. [CrossRef] [PubMed]
195. Jain, P.; Chaney, A.M.; Carlson, M.L.; Jackson, I.M.; Rao, A.; James, M.L. Neuroinflammation PET Imaging: Current Opinion andFuture Directions. J. Nucl. Med. 2020, 61, 1107–1112. [CrossRef]
196. Narayanaswami, V.; Dahl, K.; Bernard-Gauthier, V.; Josephson, L.; Cumming, P.; Vasdev, N. Emerging PET Radiotracers andTargets for Imaging of Neuroinflammation in Neurodegenerative Diseases: Outlook Beyond TSPO. Mol. Imaging 2018, 17, 1536012118792317. [CrossRef]
197. Chen, Z.; Haider, A.; Chen, J.; Xiao, Z.; Gobbi, L.; Honer, M.; Grether, U.; Arnold, S.E.; Josephson, L.; Liang, S.H. The Repertoire of Small-Molecule PET Probes for Neuroinflammation Imaging: Challenges and Opportunities beyond TSPO. J. Med. Chem. 2021, 64, 17656–17689. [CrossRef] [PubMed]
198. Zhang,W.; Sun, H.S.;Wang, X.; Dumont, A.S.; Liu, Q. Cellular senescence, DNA damage, and neuroinflammation in the aging brain. Trends Neurosci. 2024, 47, 461–474. [CrossRef] [PubMed]
199. Jin, R.; Chan, A.K.Y.;Wu, J.; Lee, T.M.C. Relationships between Inflammation and Age-Related Neurocognitive Changes. Int. J. Mol. Sci. 2022, 23, 12573. [CrossRef]
200. Gonzalez-Perez, O.; Gutierrez-Fernandez, F.; Lopez-Virgen, V.; Collas-Aguilar, J.; Quinones-Hinojosa, A.; Garcia-Verdugo, J.M. Immunological regulation of neurogenic niches in the adult brain. Neuroscience 2012, 226, 270–281. [CrossRef]
201. Das, S.; Basu, A. Inflammation: A new candidate in modulating adult neurogenesis. J. Neurosci. Res. 2008, 86, 1199–1208. [CrossRef]
202. Galea, I. The blood-brain barrier in systemic infection and inflammation. Cell Mol. Immunol. 2021, 18, 2489–2501. [CrossRef]
203. Han, J.; Harris, R.A.; Zhang, X.M. An updated assessment of microglia depletion: Current concepts and future directions. Mol. Brain 2017, 10, 25. [CrossRef] [PubMed]
204. Wu, X.; Shen, Q.; Chang, H.; Li, J.; Xing, D. Promoted CD4(+) T cell-derived IFN-γ/IL-10 by photobiomodulation therapymodulates neurogenesis to ameliorate cognitive deficits in APP/PS1 and 3xTg-AD mice. J. Neuroinflamm. 2022, 19, 253. [CrossRef]
205. Brunet, A.; Goodell, M.A.; Rando, T.A. Ageing and rejuvenation of tissue stem cells and their niches. Nat. Rev. Mol. Cell Biol. 2023, 24, 45–62. [CrossRef]
206. Parkitny, L.; Maletic-Savatic, M. Glial PAMPering and DAMPening of Adult Hippocampal Neurogenesis. Brain Sci. 2021, 11, 1299.[CrossRef] [PubMed]
207. Allen,W.E.; Blosser, T.R.; Sullivan, Z.A.; Dulac, C.; Zhuang, X. Molecular and spatial signatures of mouse brain aging at single-cell resolution. Cell 2023, 186, 194–208.e118. [CrossRef]
208. Velikic, G.; Maric, D.M.; Maric, D.L.; Supic, G.; Puletic, M.; Dulic, O.; Vojvodic, D. Harnessing the Stem Cell Niche in Regenerative Medicine: Innovative Avenue to Combat Neurodegenerative Diseases. Int. J. Mol. Sci. 2024, 25, 993. [CrossRef]
209. Duque, A.; Arellano, J.I.; Rakic, P. An assessment of the existence of adult neurogenesis in humans and value of its rodent models for neuropsychiatric diseases. Mol. Psychiatry 2022, 27, 377–382. [CrossRef]
210. Geirsdottir, L.; David, E.; Keren-Shaul, H.; Weiner, A.; Bohlen, S.C.; Neuber, J.; Balic, A.; Giladi, A.; Sheban, F.; Dutertre, C.A.; et al. Cross-Species Single-Cell Analysis Reveals Divergence of the Primate Microglia Program. Cell 2019, 179, 1609–1622.e1616. [CrossRef]
211. Lim, D.A.; Alvarez-Buylla, A. The Adult Ventricular-Subventricular Zone (V-SVZ) and Olfactory Bulb (OB) Neurogenesis. ColdSpring Harb. Perspect. Biol. 2016, 8, a018820. [CrossRef] [PubMed]
212. Denoth-Lippuner, A.; Jessberger, S. Formation and integration of new neurons in the adult hippocampus. Nat. Rev. Neurosci. 2021, 22, 223–236. [CrossRef]
213. Tosoni, G.; Ayyildiz, D.; Bryois, J.; Macnair, W.; Fitzsimons, C.P.; Lucassen, P.J.; Salta, E. Mapping human adult hippocampalneurogenesis with single-cell transcriptomics: Reconciling controversy or fueling the debate? Neuron 2023, 111, 1714–1731.e1713. [CrossRef] [PubMed]
214. Nutma, E.; Fancy, N.; Weinert, M.; Tsartsalis, S.; Marzin, M.C.; Muirhead, R.C.J.; Falk, I.; Breur, M.; de Bruin, J.; Hollaus, D.; et al. Translocator protein is a marker of activated microglia in rodent models but not human neurodegenerative diseases. Nat.Commun. 2023, 14, 5247. [CrossRef]
215. Pediaditakis, I.; Kodella, K.R.; Manatakis, D.V.; Le, C.Y.; Barthakur, S.; Sorets, A.; Gravanis, A.; Ewart, L.; Rubin, L.L.; Manolakos,E.S.; et al. A microengineered Brain-Chip to model neuroinflammation in humans. iScience 2022, 25, 104813. [CrossRef]
216. Tian, A.; Bhattacharya, A.; Muffat, J.; Li, Y. Expanding the neuroimmune research toolkit with in vivo brain organoid technologies.Dis. Model. Mech. 2025, 18, dmm052200. [CrossRef]
217. Balestri, W.; Sharma, R.; da Silva, V.A.; Bobotis, B.C.; Curle, A.J.; Kothakota, V.; Kalantarnia, F.; Hangad, M.V.; Hoorfar, M.; Jones, J.L.; et al. Modeling the neuroimmune system in Alzheimer's and Parkinson's diseases. J. Neuroinflamm. 2024, 21, 32. [CrossRef] [PubMed]
218. Tanaka, M. Parkinson's Disease: Bridging Gaps, Building Biomarkers, and Reimagining Clinical Translation. Cells 2025, 14, 1161. [CrossRef]
219. Tanaka, M.; Battaglia, S. Dualistic Dynamics in Neuropsychiatry: From Monoaminergic Modulators to Multiscale BiomarkerMaps. Biomedicines 2025, 13,

1456. [CrossRef]
220. Tanaka, M. From Monoamines to Systems Psychiatry: Rewiring Depression Science and Care (1960s–2025). Biomedicines 2025,2026, 35. [CrossRef] Takkinen, J.S.; Lopez-Picon, F.R.; Al Majidi, R.; Eskola, O.; Krzyczmonik, A.; Keller, T.; Loyttyniemi, E.; Solin, O.; Rinne, J.O.;
221. Haaparanta-Solin, M. Brain energy metabolism and neuroinflammation in ageing APP/PS1-21 mice using longitudinal (18)F-FDG and (18)F-DPA-714 PET imaging. J. Cereb. Blood Flow. Metab. 2017, 37, 2870–2882. [CrossRef]
222. Wu, Y.; Bottes, S.; Fisch, R.; Zehnder, C.; Cole, J.D.; Pilz, G.A.; Helmchen, F.; Simons, B.D.; Jessberger, S. Chronic in vivo imaging defines age-dependent alterations of neurogenesis in the mouse hippocampus. Nat. Aging 2023, 3, 380–390. [CrossRef]
223. Mathys, H.; Adaikkan, C.; Gao, F.; Young, J.Z.; Manet, E.; Hemberg, M.; De Jager, P.L.; Ransohoff, R.M.; Regev, A.; Tsai, L.H. Temporal Tracking of Microglia Activation in Neurodegeneration at Single-Cell Resolution. Cell Rep. 2017, 21, 366–380. [CrossRef] [PubMed]
224. Kreisl,W.C.; Kim, M.J.; Coughlin, J.M.; Henter, I.D.; Owen, D.R.; Innis, R.B. PET imaging of neuroinflammation in neurological disorders. Lancet Neurol. 2020, 19, 940–950. [CrossRef] [PubMed]
225. Tanaka, M. From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized NeuropsychiatricCare. Biomedicines 2025, 13, 167. [CrossRef]
226. Kamei, R.; Urata, S.; Maruoka, H.; Okabe, S. In vivo Chronic Two-Photon Imaging of Microglia in the Mouse Hippocampus. J. Vis. Exp. 2022, 185, e64104. [CrossRef] [PubMed]
227. Padmashri, R.; Tyner, K.; Dunaevsky, A. Implantation of a Cranial Window for Repeated In Vivo Imaging in Awake Mice. J. Vis. Exp. 2021. [CrossRef] [PubMed]
228. Xiong, H.; Tang, F.; Guo, Y.; Xu, R.; Lei, P. Neural circuit changes in neurological disorders: Evidence from in vivo two-photon imaging. Ageing Res. Rev. 2023, 87, 101933. [CrossRef]
229. Ulivi, A.F.; Castello-Waldow, T.P.;Weston, G.; Yan, L.; Yasuda, R.; Chen, A.; Attardo, A. Longitudinal Two-Photon Imaging ofDorsal Hippocampal CA1 in Live Mice. J. Vis. Exp. 2019. [CrossRef]
230. Ren, W.; Ji, B.; Guan, Y.; Cao, L.; Ni, R. Recent Technical Advances in Accelerating the Clinical Translation of Small Animal Brain Imaging: Hybrid Imaging, Deep Learning, and Transcriptomics. Front. Med. 2022, 9, 771982. [CrossRef] [PubMed]
231. Guglielmetti, C.; Levi, J.; Huynh, T.L.; Tiret, B.; Blecha, J.; Tang, R.; VanBrocklin, H.; Chaumeil, M.M. Longitudinal Imaging of TCells and Inflammatory Demyelination in a Preclinical Model of Multiple Sclerosis Using (18) F-FAraG PET and MRI. J. Nucl. Med. 2022, 63, 140–146. [CrossRef] [PubMed]
232. 235. Best, L.; Ghadery, C.; Pavese, N.; Tai, Y.F.; Strafella, A.P. New and Old TSPO PET Radioligands for Imaging Brain MicroglialActivation in Neurodegenerative Disease. Curr. Neurol. Neurosci. Rep. 2019, 19, 24. [CrossRef] [PubMed]
233. Schwarz, C.G. Uses of Human MR and PET Imaging in Research of Neurodegenerative Brain Diseases. Neurotherapeutics 2021, 18,661–672. [CrossRef] [PubMed]
234. Mannheim, J.G.; Schmid, A.M.; Schwenck, J.; Katiyar, P.; Herfert, K.; Pichler, B.J.; Disselhorst, J.A. PET/MRI Hybrid Systems.Semin. Nucl. Med. 2018, 48, 332–347. [CrossRef]
235. Tanaka, M.; He, Z.; Han, S.; Battaglia, S. Editorial: Noninvasive brain stimulation: A promising approach to study and improve emotion regulation. Front. Behav. Neurosci. 2025, 19, 1633936. [CrossRef]
236. Tanaka, M.; Battaglia, S.; Liloia, D. Navigating Neurodegeneration: Integrating Biomarkers, Neuroinflammation, and Imaging inParkinson's, Alzheimer's, and Motor Neuron Disorders. Biomedicines 2025, 13, 1045. [CrossRef]
237. Valotto Neto, L.J.; Reverete de Araujo, M.; Moretti Junior, R.C.; Mendes Machado, N.; Joshi, R.K.; Dos Santos Buglio, D.; BarbalhoLamas, C.; Direito, R.; Fornari Laurindo, L.;Tanaka, M.; et al. Investigating the Neuroprotective and Cognitive-Enhancing Effects of Bacopa monnieri: A Systematic Review Focused on Inflammation, Oxidative Stress, Mitochondrial Dysfunction, andApoptosis. Antioxidants 2024, 13, 393. [CrossRef]
238. Beaino, W.; Janssen, B.; Kooij, G.; van der Pol, S.M.A.; van Het Hof, B.; van Horssen, J.; Windhorst, A.D.; de Vries, H.E. Purinergic receptors P2Y12R and P2X7R: Potential targets for PET imaging of microglia phenotypes in multiple sclerosis. J. Neuroinflamm.2017, 14, 259. [CrossRef]
239. Zhou, R.; Ji, B.; Kong, Y.; Qin, L.; Ren, W.; Guan, Y.; Ni, R. PET Imaging of Neuroinflammation in Alzheimer's Disease. Front. Immunol. 2021, 12, 739130. [CrossRef]
240. Parker, C.A.; Nutt, D.J.; Tyacke, R.J. Imidazoline-I2 PET Tracers in Neuroimaging. Int. J. Mol. Sci. 2023, 24, 9787. [CrossRef][PubMed]
241. Zaharchuk, G. Next generation research applications for hybrid PET/MR and PET/CT imaging using deep learning. Eur. J. Nucl.Med. Mol. Imaging 2019, 46, 2700–2707. [CrossRef] [PubMed]
242. Aiello, M.; Cavaliere, C.; Fiorenza, D.; Duggento, A.; Passamonti, L.; Toschi, N. Neuroinflammation in NeurodegenerativeDiseases: Current Multi-modal Imaging Studies and Future Opportunities for Hybrid PET/MRI. Neuroscience 2019, 403, 125–135. [CrossRef]
243. Chiu, F.Y.; Yen, Y. Imaging biomarkers for clinical applications in neuro-oncology: Current status and future perspectives. Biomark.Res. 2023, 11, 35. [CrossRef]
244. Tanaka, M. Special Issue "Translating Molecular Psychiatry: From Biomarkers to Personalized Therapies". Int. J. Mol. Sci. 2025, 26, 10238. [CrossRef] [PubMed]
245. Fleischer, V.; Brummer, T.; Muthuraman, M.; Steffen, F.; Heldt, M.; Protopapa, M.;Schraad, M.; Gonzalez-Escamilla, G.; Groppa,S.; Bittner, S.; et al. Biomarker combinations from different modalities predict early

disability accumulation in multiple sclerosis. Front. Immunol. 2025, 16, 1532660. [CrossRef]
246. Vassal, M.; Martins, F.; Monteiro, B.; Tambaro, S.; Martinez-Murillo, R.; Rebelo, S. Emerging Pro-neurogenic Therapeutic Strategies for Neurodegenerative Diseases: A Review of Pre-clinical and Clinical Research. Mol. Neurobiol. 2025, 62, 46–76. [CrossRef]
247. Praca, C.; Rai, A.; Santos, T.; Cristov.o, A.C.; Pinho, S.L.; Cecchelli, R.; Dehouck, M.P.; Bernardino, L.; Ferreira, L.S. A nanoformulation for the preferential accumulation in adult neurogenic niches. J. Control Release 2018, 284, 57–72. [CrossRef]
248. Tanaka, M.; Tuka, B.; Vecsei, L. Navigating the Neurobiology of Migraine: From Pathways to Potential Therapies. Cells 2024, 13,1098. [CrossRef]
249. Li, X.;Wang, H.; Zhang, Q.; Sun, X.; Zhang, M.;Wang, G. Inhibition of adult hippocampal neurogenesis induced by postoperativeCD8 + T-cell infiltration is associated with cognitive decline later following surgery in adult mice. J. Neuroinflamm. 2023, 20, 227. [CrossRef] [PubMed]
250. Brocke, S.; Piercy, C.; Steinman, L.; Weissman, I.L.; Veromaa, T. Antibodies to CD44 and integrin alpha4, but not L-selectin, prevent central nervous system inflammation and experimental encephalomyelitis by blocking secondary leukocyte recruitment. Proc. Natl. Acad. Sci. USA 1999, 96, 6896–6901. [CrossRef] [PubMed]
251. Guo, J.; Tang, X.; Deng, P.; Hui, H.; Chen, B.; An, J.; Zhang, G.; Shi, K.;Wang, J.; He, Y.; et al. Interleukin-4 from curcumin-activatedOECs emerges as a central modulator for increasing M2 polarization of microglia/macrophage in OEC anti-inflammatory activity for functional repair of spinal cord injury. Cell Commun. Signal 2024, 22, 162. [CrossRef] [PubMed]
252. Marchetti, B.; Tirolo, C.; L'Episcopo, F.; Caniglia, S.; Testa, N.; Smith, J.A.; Pluchino, S.; Serapide, M.F. Parkinson's disease, aging and adult neurogenesis: Wnt/β-catenin signalling as the key to unlock the mystery of endogenous brain repair. Aging Cell 2020, 19, e13101. [CrossRef]
253. Zhu, R.; Zhu, X.; Zhu, Y.; Wang, Z.; He, X.; Wu, Z.; Xue, L.; Fan, W.; Huang, R.; Xu, Z.; et al. Immunomodulatory Layered Double Hydroxide Nanoparticles Enable Neurogenesis by Targeting Transforming Growth Factor-β Receptor 2. ACS Nano 2021, 15, 2812–2830. [CrossRef]
254. Xu, L.; Ramirez-Matias, J.; Hauptschein, M.; Sun, E.D.; Lunger, J.C.; Buckley, M.T.; Brunet, A. Restoration of neuronal progenitors by partial reprogramming in the aged neurogenic niche. Nat. Aging 2024, 4, 546–567. [CrossRef]
255. Dubey, S.; Heinen, S.; Krantic, S.; McLaurin, J.; Branch, D.R.; Hynynen, K.; Aubert, I. Clinically approved IVIg delivered to the hippocampus with focused ultrasound promotes neurogenesis in a model of Alzheimer's disease. Proc. Natl. Acad. Sci. USA 2020, 117, 32691–32700. [CrossRef]
256. Bonetto, V.; Grilli, M. Neural stem cell-derived extracellular vesicles: Mini players with key roles in neurogenesis, immunomodulation, neuroprotection and aging. Front. Mol. Biosci. 2023, 10, 1187263. [CrossRef]
257. Li, H.; Chen, G. In Vivo Reprogramming for CNS Repair: Regenerating Neurons from Endogenous Glial Cells. Neuron 2016, 91, 728–738. [CrossRef] [PubMed]
258. 261. Shinozaki, Y.; Shibata, K.; Yoshida, K.; Shigetomi, E.; Gachet, C.; Ikenaka, K.; Tanaka, K.F.; Koizumi, S. Transformation of Astrocytes to a Neuroprotective Phenotype by Microglia via P2Y(1) Receptor Downregulation. Cell Rep. 2017, 19, 1151–1164. [CrossRef] [PubMed]
259. Guo, Z.; Zhang, L.; Wu, Z.; Chen, Y.; Wang, F.; Chen, G. In vivo direct reprogramming of reactive glial cells into functionalneurons after brain injury and in an Alzheimer's disease model. Cell Stem Cell 2014, 14, 188–202. [CrossRef] Zhang, J.; Rong, P.; Zhang, L.; He, H.; Zhou, T.; Fan, Y.; Mo, L.; Zhao, Q.; Han, Y.; Li, S.; et al. IL4-driven microglia modulate stress resilience through BDNF-dependent neurogenesis. Sci. Adv. 2021, 7, eabb9888. [CrossRef]
260. Cai, B.; Seong, K.J.; Bae, S.W.; Kook, M.S.; Chun, C.; Lee, J.H.; Choi,W.S.; Jung, J.Y.; Kim,W.J.Water-Soluble Arginyl-Diosgenin Analog Attenuates Hippocampal Neurogenesis Impairment Through Blocking Microglial Activation Underlying NF-κB and JNKMAPK Signaling in Adult Mice Challenged by LPS. Mol. Neurobiol. 2019, 56, 6218–6238. [CrossRef] [PubMed]
261. Qin, R.; Lai, X.; Xu, W.; Qin, Q.; Liang, X.; Xie, M.; Chen, L. The Mechanisms and Application Prospects of Astrocyte Reprogramminginto Neurons in Central Nervous System Diseases. Curr. Neuropharmacol. 2025. [CrossRef] [PubMed]
262. Zhang, L.; Yin, J.C.; Yeh, H.; Ma, N.X.; Lee, G.; Chen, X.A.;Wang, Y.; Lin, L.; Chen, L.; Jin, P.; et al. Small Molecules Efficiently Reprogram Human Astroglial Cells into Functional Neurons. Cell Stem Cell 2015, 17, 735–747. [CrossRef] [PubMed]
263. Ma, Y.; Xie, H.; Du, X.;Wang, L.; Jin, X.; Zhang, Q.; Han, Y.; Sun, S.;Wang, L.; Li, X.; et al. In vivo chemical reprogramming of astrocytes into neurons. Cell Discov. 2021, 7, 12. [CrossRef]
264. Huang, L.; Lai, X.; Liang, X.; Chen, J.; Yang, Y.; Xu, W.; Qin, Q.; Qin, R.; Huang, X.; Xie, M.; et al. A promise for neuronal repair:Reprogramming astrocytes into neurons in vivo. Biosci. Rep. 2024, 44, BSR20231717. [CrossRef] [PubMed]
265. Revuelta, M.; Urrutia, J.; Villarroel, A.; Casis, O. Microglia-Mediated Inflammation and Neural Stem Cell Differentiation in Alzheimer's Disease: Possible Therapeutic Role of K(V)1.3 Channel Blockade. Front. Cell Neurosci. 2022, 16, 868842. [CrossRef]
266. Gres,ă, A.; Hermann, D.M.; Boboc, I.K.S.; Doeppner, T.R.; Petcu, E.; Semida, G.F.; Popa-Wagner, A. Glial Cell Reprogrammingin Ischemic Stroke: A Review of Recent Advancements and Translational Challenges. Transl. Stroke Res. 2025, 16, 1811–1835. [CrossRef]

267. Feng, X.; Li, Z.; Liu, Y.; Chen, D.; Zhou, Z. CRISPR/Cas9 technology for advancements in cancer immunotherapy: From uncovering regulatory mechanisms to therapeutic applications. Exp. Hematol. Oncol. 2024, 13, 102. [CrossRef] [PubMed]
268. Tai,W.; Xu, X.M.; Zhang, C.L. Regeneration Through in vivo Cell Fate Reprogramming for Neural Repair. Front. Cell Neurosci.2020, 14, 107. [CrossRef]
269. Mahmoudi, N.; Wang, Y.; Moriarty, N.; Ahmed, N.Y.; Dehorter, N.; Lisowski, L.; Harvey, A.R.; Parish, C.L.; Williams, R.J.; Nisbet, D.R. Neuronal Replenishment via Hydrogel-Rationed Delivery of Reprogramming Factors. ACS Nano 2024, 18, 3597–3613. [CrossRef]
270. 274. Zhao, Z.; Wang, Y.; Zhou, R.; Li, Y.; Gao, Y.; Tu, D.; Wilson, B.; Song, S.; Feng, J.; Hong, J.S.; et al. A novel role of NLRP3-generated IL-1β in the acute-chronic transition of peripheral lipopolysaccharide-elicited neuroinflammation: Implications for sepsis-associated neurodegeneration. J. Neuroinflamm. 2020, 17, 64. [CrossRef] [PubMed]
271. Harrison, D.; Billinton, A.; Bock, M.G.; Doedens, J.R.; Gabel, C.A.; Holloway, M.K.; Porter, R.A.; Reader, V.; Scanlon, J.; Schooley,K.; et al. Discovery of Clinical Candidate NT-0796, a Brain-Penetrant and Highly Potent NLRP3 Inflammasome Inhibitor for Neuroinflammatory Disorders. J. Med. Chem. 2023, 66, 14897–14911. [CrossRef] [PubMed]
272. Ward, R.; Li, W.; Abdul, Y.; Jackson, L.; Dong, G.; Jamil, S.; Filosa, J.; Fagan, S.C.; Ergul, A. NLRP3 inflammasome inhibition with MCC950 improves diabetes-mediated cognitive impairment and vasoneuronal remodeling after ischemia. Pharmacol. Res. 2019, 142, 237–250. [CrossRef] [PubMed]
273. Gordon, R.; Albornoz, E.A.; Christie, D.C.; Langley, M.R.; Kumar, V.; Mantovani, S.; Robertson, A.A.B.; Butler, M.S.; Rowe, D.B.; O'Neill, L.A.; et al. Inflammasome inhibition prevents α-synuclein pathology and dopaminergic neurodegeneration in mice. Sci. Transl. Med. 2018, 10, eaah4066. [CrossRef]
274. Dempsey, C.; Rubio Araiz, A.; Bryson, K.J.; Finucane, O.; Larkin, C.; Mills, E.L.; Robertson, A.A.B.; Cooper, M.A.; O'Neill, L.A.J.; Lynch, M.A. Inhibiting the NLRP3 inflammasome with MCC950 promotes non-phlogistic clearance of amyloid-β and cognitive function in APP/PS1 mice. Brain Behav. Immun. 2017, 61, 306–316. [CrossRef] [PubMed]
275. Mackay, A.; Velcicky, J.; Gommermann, N.; Mattes, H.; Janser, P.;Wright, M.; Dubois, C.; Brenneisen, S.; Ilic, S.; Vangrevelinghe, E.; et al. Discovery of NP3-253, a Potent Brain Penetrant Inhibitor of the NLRP3 Inflammasome. J. Med. Chem. 2024, 67, 20780–20798.
276. Kuwar, R.; Rolfe, A.; Di, L.; Blevins, H.; Xu, Y.; Sun, X.; Bloom, G.S.; Zhang, S.; Sun, D. A Novel Inhibitor Targeting NLRP3Inflammasome Reduces Neuropathology and Improves Cognitive Function in Alzheimer's Disease Transgenic Mice. J. AlzheimersDis. 2021, 82, 1769–1783. [CrossRef] [PubMed]
277. Barbalho, S.M.; Laurindo, L.F.; de Oliveira Zanuso, B.; da Silva, R.M.S.; Gallerani Caglioni, L.; Nunes Junqueira de Moraes,V.B.F.; Fornari Laurindo, L.; Dogani Rodrigues, V.; da Silva Camarinha Oliveira, J.; Beluce, M.E.; et al. AdipoRon's Impact onAlzheimer's Disease-A Systematic Review and Meta-Analysis. Int. J. Mol. Sci. 2025, 26, 484. [CrossRef] [PubMed]
278. Xu, Y.; Yang, Y.; Chen, X.; Jiang, D.; Zhang, F.; Guo, Y.; Hu, B.; Xu, G.; Peng, S.;Wu, L.; et al. NLRP3 inflammasome in cognitive impairment and pharmacological properties of its inhibitors. Transl. Neurodegener. 2023, 12, 49. [CrossRef] [PubMed]
279. McManus, R.M.; Latz, E. NLRP3 inflammasome signalling in Alzheimer's disease. Neuropharmacology 2024, 252, 109941. [CrossRef]
280. Stonesifer, C.; Corey, S.; Ghanekar, S.; Diamandis, Z.; Acosta, S.A.; Borlongan, C.V. Stem cell therapy for abrogating stroke-induced neuroinflammation and relevant secondary cell death mechanisms. Prog. Neurobiol. 2017, 158, 94–131. [CrossRef]
281. Ma, Y.; Yang, S.; He, Q.; Zhang, D.; Chang, J. The Role of Immune Cells in Post-Stroke Angiogenesis and Neuronal Remodeling: The Known and the Unknown. Front. Immunol. 2021, 12, 784098. [CrossRef]
282. Nakagomi, T.; Takagi, T.; Beppu, M.; Yoshimura, S.; Matsuyama, T. Neural regeneration by regionally induced stem cells within post-stroke brains: Novel therapy perspectives for stroke patients. World J. Stem Cells 2019, 11, 452–463. [CrossRef]
283. Ismael, S.; Zhao, L.; Nasoohi, S.; Ishrat, T. Inhibition of the NLRP3-inflammasome as a potential approach for neuroprotectionafter stroke. Sci. Rep. 2018, 8, 5971. [CrossRef]
284. Bellut, M.; Bieber, M.; Kraft, P.; Weber, A.N.R.; Stoll, G.; Schuhmann, M.K. Delayed NLRP3 inflammasome inhibition ameliorates subacute stroke progression in mice. J. Neuroinflamm. 2023, 20, 4. [CrossRef] [PubMed]
285. Patnala, R.; Arumugam, T.V.; Gupta, N.; Dheen, S.T. HDAC Inhibitor Sodium Butyrate-Mediated Epigenetic Regulation Enhances Neuroprotective Function of Microglia During Ischemic Stroke. Mol. Neurobiol. 2017, 54, 6391–6411. [CrossRef] [PubMed]
286. Jayaraj, K.; Kumar, R.; Shyamasundar, S.; Arumugam, T.V.; Polepalli, J.S.; Dheen, S.T. Spatial Transcriptomic Analysis Reveals HDAC Inhibition Modulates Microglial Dynamics to Protect Against Ischemic Stroke in Mice. Glia 2025, 73, 1817–1840. [CrossRef] [PubMed]
287. Vande Walle, L.; Lamkanfi, M. Drugging the NLRP3 inflammasome: From signalling mechanisms to therapeutic targets. Nat. Rev.Drug Discov. 2024, 23, 43–66. [CrossRef]
288. Mammoliti, O.; Carbajo, R.; Perez-Benito, L.; Yu, X.; Prieri, M.L.C.; Bontempi, L.; Embrechts, S.; Paesmans, I.; Bassi, M.;Bhattacharya, A.; et al. Discovery of Potent and Brain-Penetrant Bicyclic NLRP3 Inhibitors with Peripheral and Central In Vivo Activity. J. Med. Chem. 2025, 68, 4848–4887. [CrossRef]
289. Barczuk, J.; Siwecka, N.; Lusa,W.; Rozp¸edek-Kami´nska,W.; Kucharska, E.; Majsterek, I. Targeting NLRP3-Mediated Neuroinflammation in Alzheimer's Disease Treatment. Int. J. Mol. Sci. 2022, 23, 8979. [CrossRef]

290. Cai, R.; Lv, R.; Shi, X.; Yang, G.; Jin, J. CRISPR/dCas9 Tools: Epigenetic Mechanism and Application in Gene TranscriptionalRegulation. Int. J. Mol. Sci. 2023, 24, 14865. [CrossRef]
291. Liu, X.S.; Wu, H.; Ji, X.; Stelzer, Y.; Wu, X.; Czauderna, S.; Shu, J.; Dadon, D.; Young, R.A.; Jaenisch, R. Editing DNA Methylationin the Mammalian Genome. Cell 2016, 167, 233–247.e217. [CrossRef]
292. O'Geen, H.; Ren, C.; Nicolet, C.M.; Perez, A.A.; Halmai, J.; Le, V.M.; Mackay, J.P.; Farnham, P.J.; Segal, D.J. dCas9-basedepigenome editing suggests acquisition of histone methylation is not sufficient for target gene repression. Nucleic Acids Res. 2017, 45, 9901–9916. [CrossRef]
293. Vojta, A.; Dobrini´c, P.; Tadi´c, V.; Bo˘ckor, L.; Kora´c, P.; Julg, B.; Klasi´c, M.; Zoldoš, V. Repurposing the CRISPR-Cas9 system for targeted DNA methylation. Nucleic Acids Res. 2016, 44, 5615–5628. [CrossRef]
294. Lu, Y.; Brommer, B.; Tian, X.; Krishnan, A.; Meer, M.;Wang, C.; Vera, D.L.; Zeng, Q.; Yu, D.; Bonkowski, M.S.; et al. Reprogramming to recover youthful epigenetic information and restore vision. Nature 2020, 588, 124–129. [CrossRef]
295. Nunez, J.K.; Chen, J.; Pommier, G.C.; Cogan, J.Z.; Replogle, J.M.; Adriaens, C.; Ramadoss, G.N.; Shi, Q.; Hung, K.L.; Samelson, A.J.; et al. Genome-wide programmable transcriptional memory by CRISPR-based epigenome editing. Cell 2021, 184, 2503–2519.e2517. [CrossRef]
296. Pattali, R.K.; Ornelas, I.J.; Nguyen, C.D.; Xu, D.; Divekar, N.S.; Nunez, J.K. CRISPRoff epigenetic editing for programmable gene silencing in human cells without DNA breaks. bioRxiv 2024. [CrossRef]
297. Yim, Y.Y.; Teague, C.D.; Nestler, E.J. In vivo locus-specific editing of the neuroepigenome. Nat. Rev. Neurosci. 2020, 21, 471–484. [CrossRef]
298. Xiong, K.; Wang, X.; Feng, C.; Zhang, K.; Chen, D.; Yang, S. Vectors in CRISPR Gene Editing for Neurological Disorders: Challenges and Opportunities. Adv. Biol. 2025, 9, e2400374. [CrossRef]
299. Shang, J.; Song, F.; Zhang, Z.; Chen, D.; Yang, S. Application of novel CRISPR tools in brain therapy. Life Sci. 2024, 352, 122855. [CrossRef]
300. Arellano, J.I.; Rakic, P. Modelling adult neurogenesis in the aging rodent hippocampus: A midlife crisis. Front. Neurosci. 2024, 18, 1416460. [CrossRef] [PubMed]
301. Darsalia, V.; Heldmann, U.; Lindvall, O.; Kokaia, Z. Stroke-induced neurogenesis in aged brain. Stroke 2005, 36, 1790–1795. [CrossRef]
302. Simard, S.; Matosin, N.; Mechawar, N. Adult Hippocampal Neurogenesis in the Human Brain: Updates, Challenges, and Perspectives. Neuroscientist 2025, 31, 141–158. [CrossRef]
303. Kuhn, H.G.; Toda, T.; Gage, F.H. Adult Hippocampal Neurogenesis: A Coming-of-Age Story. J. Neurosci. 2018, 38, 10401–10410. 297.
304. Kempermann, G.; Gage, F.H.; Aigner, L.; Song, H.; Curtis, M.A.; Thuret, S.; Kuhn, H.G.; Jessberger, S.; Frankland, P.W.; Cameron, H.A.; et al. Human Adult Neurogenesis: Evidence and Remaining Questions. Cell Stem Cell 2018, 23, 25–30. [CrossRef] [PubMed]
305. Holtman, I.R.; Raj, D.D.; Miller, J.A.; Schaafsma, W.; Yin, Z.; Brouwer, N.; Wes, P.D.; Moller, T.; Orre, M.; Kamphuis, W.; et al. Induction of a common microglia gene expression signature by aging and neurodegenerative conditions: A co-expression meta-analysis. Acta Neuropathol. Commun. 2015, 3, 31. [CrossRef]
306. Flowers, A.; Bell-Temin, H.; Jalloh, A.; Stevens, S.M., Jr.; Bickford, P.C. Proteomic anaysis of aged microglia: Shifts in transcription, bioenergetics, and nutrient response. J. Neuroinflamm. 2017, 14, 96. [CrossRef]
307. Galatro, T.F.; Holtman, I.R.; Lerario, A.M.; Vainchtein, I.D.; Brouwer, N.; Sola, P.R.; Veras, M.M.; Pereira, T.F.; Leite, R.E.P.; Moller, T.; et al. Transcriptomic analysis of purified human cortical microglia reveals age-associated changes. Nat. Neurosci. 2017, 20, 1162–1171. [CrossRef]
308. He, R.; Zhang, Q.;Wang, L.; Hu, Y.; Qiu, Y.; Liu, J.; You, D.; Cheng, J.; Cao, X. Exploring the feasibility of using mice as a substitute model for investigating microglia in aging and Alzheimer's disease though single cell analysis. PLoS ONE 2024, 19, e0311374. [CrossRef]
309. Qi, C.; Yan, Y.; Cao, Q.; Zou, L.; Li, S.; Yang, Q.; Deng, Q.; Wu, B.; Song, B. Elucidating the mechanisms underlying astrocytemicroglia crosstalk in hippocampal neuroinflammation induced by acute diquat exposure. Environ. Sci. Pollut. Res. Int. 2024, 31,15746–15758. [CrossRef]
310. Hou, B.; Zhang, Y.; Liang, P.; He, Y.; Peng, B.; Liu,W.; Han, S.; Yin, J.; He, X. Inhibition of the NLRP3-inflammasome prevents cognitive deficits in experimental autoimmune encephalomyelitis mice via the alteration of astrocyte phenotype. Cell Death Dis. 2020, 11, 377. [CrossRef]
311. Anderson, F.L.; Biggs, K.E.; Rankin, B.E.; Havrda, M.C. NLRP3 inflammasome in neurodegenerative disease. Transl. Res. 2023,252, 21–33. [CrossRef] [PubMed]
312. Adamczak, S.; Dale, G.; de Rivero Vaccari, J.P.; Bullock, M.R.; Dietrich,W.D.; Keane, R.W. Inflammasome proteins in cerebrospinal fluid of brain-injured patients as biomarkers of functional outcome: Clinical article. J. Neurosurg. 2012, 117, 1119–1125. [CrossRef]
313. Chou, V.; Pearse, R.V., 2nd; Aylward, A.J.; Ashour, N.; Taga, M.; Terzioglu, G.; Fujita, M.; Fancher, S.B.; Sigalov, A.; Benoit, C.R.;et al. INPP5D regulates inflammasome activation in human microglia. Nat. Commun. 2023, 14, 7552. [CrossRef]
314. Ma, C.L.; Ma, X.T.; Wang, J.J.; Liu, H.; Chen, Y.F.; Yang, Y. Physical exercise induces hippocampal neurogenesis and prevents cognitive decline. Behav. Brain Res. 2017, 317, 332–339. [CrossRef] [PubMed]
315. Figueiredo Godoy, A.C.; Frota, F.F.; Araujo, L.P.; Valenti, V.E.; Pereira, E.; Detregiachi, C.R.P.; Galhardi, C.M.; Caracio, F.C.; Haber,R.S.A.; Fornari Laurindo, L.; et al. Neuroinflammation and Natural Antidepressants: Balancing Fire with Flora. Biomedicines 2025,13, 1129. [CrossRef]
316. Zhao, R.; Tian, X.; Xu, H.;Wang, Y.; Lin, J.;Wang, B. Aerobic Exercise Restores Hippocampal Neurogenesis and Cognitive Functionby Decreasing Microglia Inflammasome Formation Through Irisin/NLRP3 Pathway. Aging Cell 2025, 24, e70061. [CrossRef]

317. Mohd Sahini, S.N.; Mohd Nor Hazalin, N.A.; Srikumar, B.N.; Jayasingh Chellammal, H.S.; Surindar Singh, G.K. Environmentalenrichment improves cognitive function, learning, memory and anxiety-related behaviours in rodent models of dementia: Implications for future study. Neurobiol. Learn. Mem. 2024, 208, 107880. [CrossRef] [PubMed]
318. Methi, A.; Islam, M.R.; Kaurani, L.; Sakib, M.S.; Kruger, D.M.; Pena, T.; Burkhardt, S.; Liebetanz, D.; Fischer, A. A Single-CellTranscriptomic Analysis of the Mouse Hippocampus After Voluntary Exercise. Mol. Neurobiol. 2024, 61, 5628–5645. [CrossRef]
319. Choi, S.H.; Bylykbashi, E.; Chatila, Z.K.; Lee, S.W.; Pulli, B.; Clemenson, G.D.; Kim, E.; Rompala, A.; Oram, M.K.; Asselin, C.; et al. Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. Science 2018, 361, eaan8821. [CrossRef]
320. Phillips, C. Lifestyle Modulators of Neuroplasticity: How Physical Activity, Mental Engagement, and Diet Promote Cognitive Health during Aging. Neural Plast. 2017, 2017, 3589271. [CrossRef]
321. Asthana, A.; Tripathi, S.; Agarwal, R. Role of Nonsteroidal Anti-Inflammatory Drugs as a Protective Factor in Alzheimer'sDisease: A Systematic Review and Meta-Analysis. Neurol. India 2024, 72, 1144–1151. [CrossRef]
322. Rivers-Auty, J.; Mather, A.E.; Peters, R.; Lawrence, C.B.; Brough, D. Anti-inflammatories in Alzheimer's disease-potential therapyor spurious correlate? Brain Commun. 2020, 2, fcaa109. [CrossRef] [PubMed]
323. Cetin, A.; Komai, S.; Eliava, M.; Seeburg, P.H.; Osten, P. Stereotaxic gene delivery in the rodent brain. Nat. Protoc. 2006, 1, 3166–3173. [CrossRef] [PubMed]
324. Kalincik, T.; Roos, I.; Sharmin, S. Observational studies of treatment effectiveness in neurology. Brain 2023, 146, 4799–4808. [CrossRef] [PubMed]
325. Uff, C.E.G.; Patel, K.; Yeung, C.; Yip, P.K. Advances in Visualizing Microglial Cells in Human Central Nervous System Tissue. Biomolecules 2022, 12, 603. [CrossRef]
326. Barnhart, A.J.; Dierickx, K. A Tale of Two Chimeras: Applying the Six Principles to Human Brain Organoid Xenotransplantation.Camb. Q. Healthc. Ethics 2023, 32, 555–571. [CrossRef]
327. Erler, A. Human brain organoid transplantation: Testing the foundations of animal research ethics. Neuroethics 2024, 17, 20.
328. Neziri, S.; Koseo˘ glu, A.E.; Deniz Koseo˘ glu, G.; Ozgultekin, B.; Ozgenturk, N. Animal models in neuroscience with alternativeapproaches: Evolutionary, biomedical, and ethical perspectives. Animal Model. Exp. Med. 2024, 7, 868–880. [CrossRef]
329. Mrza, M.A.; He, J.;Wang, Y. Integration of iPSC-Derived Microglia into Brain Organoids for Neurological Research. Int. J. Mol.Sci. 2024, 25, 3148. [CrossRef]
330. Schafer, S.T.; Mansour, A.A.; Schlachetzki, J.C.M.; Pena, M.; Ghassemzadeh, S.; Mitchell, L.; Mar, A.; Quang, D.; Stumpf, S.; Ortiz,I.S.; et al. An in vivo neuroimmune organoid model to study human microglia phenotypes. Cell 2023, 186, 2111–2126.e2120.[CrossRef]
331. Ao, Z.; Cai, H.;Wu, Z.; Song, S.; Karahan, H.; Kim, B.; Lu, H.C.; Kim, J.; Mackie, K.; Guo, F. Tubular human brain organoids tomodel microglia-mediated neuroinflammation. Lab. Chip 2021, 21, 2751–2762. [CrossRef]
332. Pagotto, G.L.O.; Santos, L.; Osman, N.; Lamas, C.B.; Laurindo, L.F.; Pomini, K.T.; Guissoni, L.M.; Lima, E.P.; Goulart, R.A.;Catharin, V.; et al. Ginkgo biloba: A Leaf of Hope in the Fight against Alzheimer's Dementia: Clinical Trial Systematic Review. Antioxidants 2024, 13, 651. [CrossRef] [PubMed]
333. Gonzales, M.M.; Garbarino, V.R.; Pollet, E.; Palavicini, J.P.; Kellogg, D.L., Jr.; Kraig, E.; Orr, M.E. Biological aging processesunderlying cognitive decline and neurodegenerative disease. J. Clin. Investig. 2022, 132, e158453. [CrossRef] [PubMed]
334. Tanaka, M.; Vecsei, L. Revolutionizing our understanding of Parkinson's disease: Dr. Heinz Reichmann's pioneering researchand future research direction. J. Neural Transm. 2024, 131, 1367–1387. [CrossRef]
335. Rao, R.V.; Subramaniam, K.G.; Gregory, J.; Bredesen, A.L.; Coward, C.; Okada, S.; Kelly, L.; Bredesen, D.E. Rationale for aMulti-Factorial Approach for the Reversal of Cognitive Decline in Alzheimer's Disease and MCI: A Review. Int. J. Mol. Sci. 2023, 24, 1659. [CrossRef] [PubMed]
336. Fekonja, L.S.; Forkel, S.J.; Aydogan, D.B.; Lioumis, P.; Cacciola, A.; Lucas, C.W.; Tournier, J.D.; Vergani, F.; Ritter, P.; Schenk, R.;et al. Translational network neuroscience: Nine roadblocks and possible solutions. Netw. Neurosci. 2025, 9, 352–370. [CrossRef]
337. Barron, H.C.; Mars, R.B.; Dupret, D.; Lerch, J.P.; Sampaio-Baptista, C. Cross-species neuroscience: Closing the explanatory gap.Philos. Trans. R. Soc. Lond. B Biol. Sci. 2021, 376, 20190633. [CrossRef]
338. Moreno-Gonzalez, I.; Garcia-Martin, J.; Marongiu, R. Editorial: Animal models of Alzheimer's disease and other dementias: Past,present, and future. Front. Aging Neurosci. 2024, 16, 1539837. [CrossRef]
339. Vitek, M.P.; Araujo, J.A.; Fossel, M.; Greenberg, B.D.; Howell, G.R.; Rizzo, S.J.S.; Seyfried, N.T.; Tenner, A.J.; Territo, P.R.;Windisch,
340. M.; et al. Translational animal models for Alzheimer's disease: An Alzheimer's Association Business Consortium Think Tank. Alzheimers Dement. 2020, 6, e12114. [CrossRef]
341. Sun, N.; Victor, M.B.; Park, Y.P.; Xiong, X.; Scannail, A.N.; Leary, N.; Prosper, S.; Viswanathan, S.; Luna, X.; Boix, C.A.; et al. Human microglial state dynamics in Alzheimer's disease progression. Cell 2023, 186, 4386–4403.e4329. [CrossRef] [PubMed]
342. Szabo, A.; Galla, Z.; Spekker, E.; Sz˝ ucs, M.; Martos, D.; Takeda, K.; Ozaki, K.; Inoue, H.; Yamamoto, S.; Toldi, J.; et al. Oxidative and Excitatory Neurotoxic Stresses in CRISPR/Cas9-Induced Kynurenine Aminotransferase Knockout Mice: A Novel Model for Despair-Based Depression and Post-Traumatic Stress Disorder. Front.

Biosci. 2025, 30, 25706. [CrossRef]
343. Pluvinage, J.V.; Wyss-Coray, T. Systemic factors as mediators of brain homeostasis, ageing and neurodegeneration. Nat. Rev.Neurosci. 2020, 21, 93–102. [CrossRef]
344. Szabo, A.; Galla, Z.; Spekker, E.; Martos, D.; Sz˝ ucs, M.; Fejes-Szabo, A.; Feher, A.; Takeda, K.; Ozaki, K.; Inoue, H.; et al. Behavioral Balance in Tryptophan Turmoil: Regional Metabolic Rewiring in Kynurenine Aminotransferase II Knockout Mice. Cells 2025, 14,1711. [CrossRef] [PubMed]
345. Higgins-Chen, A.T.; Thrush, K.L.; Levine, M.E. Aging biomarkers and the brain. Semin. Cell Dev. Biol. 2021, 116, 180–193. [CrossRef] [PubMed]
346. Sun, X.-Y.; Ju, X.-C.; Li, Y.; Zeng, P.-M.; Wu, J.; Zhou, Y.-Y.; Shen, L.-B.; Dong, J.; Chen, Y.-J.; Luo, Z.-G. Generation of vascularized brain organoids to study neurovascular interactions. elife 2022, 11, e76707. [CrossRef]
347. Martos, D.; L˝orinczi, B.; Szatmari, I.; Vecsei, L.; Tanaka, M. Decoupling Behavioral Domains via Kynurenic Acid AnalogOptimization: Implications for Schizophrenia and Parkinson's Disease Therapeutics. Cells 2025, 14, 973. [CrossRef]
348. Lei, T.; Zhang, X.; Fu, G.; Luo, S.; Zhao, Z.; Deng, S.; Li, C.; Cui, Z.; Cao, J.; Chen, P.; et al. Advances in human cellular mechanisticunderstanding and drug discovery of brain organoids for neurodegenerative diseases. Ageing Res. Rev. 2024, 102, 102517. [CrossRef] [PubMed]
349. Tanaka, M.; Battaglia, S.; Gimenez-Llort, L.; Chen, C.; Hepsomali, P.; Avenanti, A.; Vecsei, L. Innovation at the Intersection:Emerging Translational Research in Neurology and Psychiatry. Cells 2024, 13, 790. [CrossRef]
350. Ngandu, T.; Lehtisalo, J.; Korkki, S.; Solomon, A.; Coley, N.; Antikainen, R.; Backman, L.; Hanninen, T.; Lindstrom, J.; Laatikainen, T.; et al. The effect of adherence on cognition in a multidomain lifestyle intervention (FINGER). Alzheimers Dement. 2022, 18,1325–1334. [CrossRef]
351. Polis, B.; Samson, A.O. Addressing the Discrepancies Between Animal Models and Human Alzheimer's Disease Pathology: Implications for Translational Research. J. Alzheimers Dis. 2024, 98, 1199–1218. [CrossRef] [PubMed]
352. Young, P.N.E.; Estarellas, M.; Coomans, E.; Srikrishna, M.; Beaumont, H.; Maass, A.; Venkataraman, A.V.; Lissaman, R.; Jimenez,D.; Betts, M.J.; et al. Imaging biomarkers in neurodegeneration: Current and future practices. Alzheimers Res. Ther. 2020, 12, 49. [CrossRef]
353. Wagatsuma, K.; Miwa, K.; Akamatsu, G.; Yamao, T.; Kamitaka, Y.; Sakurai, M.; Fujita, N.; Hanaoka, K.; Matsuda, H.; Ishii, K.Toward standardization of tau PET imaging corresponding to various tau PET tracers: A multicenter phantom study. Ann. Nucl. Med. 2023, 37, 494–503. [CrossRef] [PubMed]
354. Juttner, J.; Szabo, A.; Gross-Scherf, B.; Morikawa, R.K.; Rompani, S.B.; Hantz, P.; Szikra, T.; Esposti, F.; Cowan, C.S.; Bharioke, A.;et al. Targeting neuronal and glial cell types with synthetic promoter AAVs in mice, non-human primates and humans. Nat. Neurosci. 2019, 22, 1345–1356. [CrossRef]
355. Tanaka, M.; Szatmari, I.; Vecsei, L. Quinoline Quest: Kynurenic Acid Strategies for Next-Generation Therapeutics via RationalDrug Design. Pharmaceuticals 2025, 18, 607. [CrossRef] [PubMed]
356. Naeem, A.; Prakash, R.; Kumari, N.; Ali Khan, M.; Quaiyoom Khan, A.; Uddin, S.; Verma, S.; Ab Robertson, A.; Boltze, J.; Shadab Raza, S. MCC950 reduces autophagy and improves cognitive function by inhibiting NLRP3-dependent neuroinflammation in arat model of Alzheimer's disease. Brain Behav. Immun. 2024, 116, 70–84. [CrossRef] [PubMed]
357. Meneghini, V.; Peviani, M.; Luciani, M.; Zambonini, G.; Gritti, A. Delivery Platforms for CRISPR/Cas9 Genome Editing of Glial Cells in the Central Nervous System. Front. Genome Ed. 2021, 3, 644319. [CrossRef]
358. Shi, L.; Li, S.; Zhu, R.; Lu, C.; Xu, X.; Li, C.; Huang, X.; Zhao, X.; Mao, F.; Li, K. CRISPRepi: A multi-omic atlas for CRISPR-basedepigenome editing. Nucleic Acids Res. 2025, 53, D901–D913. [CrossRef]
359. Grinan-Ferre, C.; Bellver-Sanchis, A.; Guerrero, A.; Pallàs, M. Advancing personalized medicine in neurodegenerative diseases:The role of epigenetics and pharmacoepigenomics in pharmacotherapy. Pharmacol. Res. 2024, 205, 107247. [CrossRef]
360. Ahmad, S.R.; Zeyaullah, M.; Khan, M.S.; AlShahrani, A.M.; Altijani, A.A.G.; Ali, H.; Dawria, A.; Mohieldin, A.; Alam, M.S.;Mohamed, A.O.A. Pharmacogenomics for neurodegenerative disorders—A focused review. Front. Pharmacol. 2024, 15, 1478964. [CrossRef]
361. Deng, S.; Xie, H.; Xie, B. Cell-based regenerative and rejuvenation strategies for treating neurodegenerative diseases. Stem CellRes. Ther. 2025, 16, 167. [CrossRef]
362. Ueda, J.; Yamazaki, T.; Funakoshi, H. Toward the Development of Epigenome Editing-Based Therapeutics: Potentials andChallenges. Int. J. Mol. Sci. 2023, 24, 4778. [CrossRef]
363. Khoshandam, M.; Soltaninejad, H.; Mousazadeh, M.; Hamidieh, A.A.; Hosseinkhani, S. Clinical applications of the CRISPR/Cas9genome-editing system: Delivery options and challenges in precision medicine. Genes. Dis. 2024, 11, 268–282. [CrossRef] [PubMed]
364. Pei,W.D.; Zhang, Y.; Yin, T.L.; Yu, Y. Epigenome editing by CRISPR/Cas9 in clinical settings: Possibilities and challenges. Brief.Funct. Genom. 2020, 19, 215–228. [CrossRef]
365. Tremblay, F.; Xiong, Q.; Shah, S.S.; Ko, C.W.; Kelly, K.; Morrison, M.S.; Giancarlo, C.; Ramirez, R.N.; Hildebrand, E.M.; Voytek,S.B.; et al. A potent epigenetic editor targeting human PCSK9 for durable reduction of low-density lipoprotein cholesterol levels. Nat. Med. 2025, 31, 1329–1338. [CrossRef] [PubMed]
366. Gemberling, M.P.; Siklenka, K.; Rodriguez, E.; Tonn-Eisinger, K.R.; Barrera, A.; Liu, F.; Kantor, A.; Li, L.; Cigliola, V.; Hazlett, M.F.;et al. Transgenic mice for in vivo epigenome editing with CRISPR-based systems. Nat. Methods 2021, 18, 965–974. [CrossRef] [PubMed]
367. Wang, F.; Cheng, L.; Zhang, X. Reprogramming Glial Cells into Functional Neuronsfor Neuro-regeneration:

Challenges andPromise. Neurosci. Bull. 2021, 37, 1625–1636. [CrossRef] [PubMed]
368. Lentini, C.; d'Orange, M.; Marichal, N.; Trottmann, M.M.; Vignoles, R.; Foucault, L.; Verrier, C.; Massera, C.; Raineteau, O.;Conzelmann, K.K.; et al. Reprogramming reactive glia into interneurons reduces chronic seizure activity in a mouse model of mesial temporal lobe epilepsy. Cell Stem Cell 2021, 28, 2104–2121.e2110. [CrossRef]
369. Matt, S.M.; Johnson, R.W. Neuro-immune dysfunction during brain aging: New insights in microglial cell regulation. Curr. Opin.Pharmacol. 2016, 26, 96–101. [CrossRef]
370. Filgueira, L.; Larionov, A.; Lannes, N. The Influence of Virus Infection on Microglia and Accelerated Brain Aging. Cells 2021, 10,1836. [CrossRef]
371. Flick, C.; Zamani, E.D.; Stahl, B.C.; Brem, A. The future of ICT for health and ageing: Unveiling ethical and social issues throughhorizon scanning foresight. Technol. Forecast. Soc. Change 2020, 155, 119995. [CrossRef]
372. Hansson, O. Biomarkers for neurodegenerative diseases. Nat. Med. 2021, 27, 954–963. [CrossRef] [PubMed]
373. Husain, M. Smarter adaptive platform clinical trials in neurology. Brain 2022, 145, 409–410. [CrossRef]
374. Grill, J.D.; Karlawish, J. Implications of FDA Approval of a First Disease-Modifying Therapy for a Neurodegenerative Disease onthe Design of Subsequent Clinical Trials. Neurology 2021, 97, 496–500. [CrossRef] [PubMed]
375. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. An Update on Genome Editing With the Utilization of CRISPR/Cas 9 System for Evaluation and Treatment of Human Diseases-A Systemic Review. J Gene Eng. Bio Res, 3(2), 15-28.
376. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. (). ''An update on Brain organoids Generation and the Advancements made in the Context of a HumanModel of Neurological Disorders-A systematic review''. Journal of Biomedical Engineering and Medical Imaging, 2021;8(6). 31-63. URL: http://dx.doi.org/10.14738/jbemi.86.11270
377. Fumagalli, M.; Lombardi, M.; Gressens, P.; Verderio, C. How to reprogram microglia toward beneficial functions. Glia 2018, 66, 2531–2549. [CrossRef] [PubMed]
378. Liang, T.; Zhang, Y.; Wu, S.; Chen, Q.; Wang, L. The Role of NLRP3 Inflammasome in Alzheimer's Disease and PotentialTherapeutic Targets. Front. Pharmacol. 2022, 13, 845185. [CrossRef]
379. Joseph E, Kunze LH, Schaefer R, Palumbo G, Kugelmann B, Wagner S, Lammich S, Feederle R, Willem M, Werner RA, Brendel M, Lindner S Design, Synthesis and Preclinical Evaluation of a Brain-Permeable PET Tracer for P2Y12 Receptor Imaging in the Brain J Med Chem. 2025 Aug 14;68(15):15543-15562. doi: 10.1021/acs.jmedchem.5c00457.