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Current understanding and prospects for targeting neurogenesis in the treatment of cognitive impairment

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From the Contents

Abstract

Adult hippocampal neurogenesis is linked to memory formation in the adult brain, with new neurons in the hippocampus exhibiting greater plasticity during their immature stages compared to mature neurons. Abnormal adult hippocampal neurogenesis is closely associated with cognitive impairment in central nervous system diseases. Targeting and regulating adult hippocampal neurogenesis have been shown to improve cognitive deficits. This review aims to expand the current understanding and prospects of targeting neurogenesis in the treatment of cognitive impairment. Recent research indicates the presence of abnormalities in AHN in several diseases associated with cognitive impairment, including cerebrovascular diseases, Alzheimer's disease, aging-related conditions, and issues related to anesthesia and surgery. The role of these abnormalities in the cognitive deficits caused by these diseases has been widely recognized, and targeting AHN is considered a promising approach for treating cognitive impairment. However, the underlying mechanisms of this role are not yet fully understood, and the effectiveness of targeting abnormal adult hippocampal neurogenesis for treatment remains limited, with a need for further development of treatment methods and detection techniques. By reviewing recent studies, we classify the potential mechanisms of adult hippocampal neurogenesis abnormalities into four categories: immunity, energy metabolism, aging, and pathological states. In immunity-related mechanisms, abnormalities in meningeal, brain, and peripheral immunity can disrupt normal adult hippocampal neurogenesis. Lipid metabolism and mitochondrial function disorders are significant energy metabolism factors that lead to abnormal adult hippocampal neurogenesis. During aging, the inflammatory state of the neurogenic niche and the expression of aging-related microRNAs contribute to reduced adult hippocampal neurogenesis and cognitive impairment in older adult patients. Pathological states of the body and emotional disorders may also result in abnormal adult hippocampal neurogenesis. Among the current strategies used to enhance this form of neurogenesis, physical therapies such as exercise, transcutaneous electrical nerve stimulation, and enriched environments have proven effective. Dietary interventions, including energy intake restriction and nutrient optimization, have shown efficacy in both basic research and clinical trials. However, drug treatments, such as antidepressants and stem cell therapy, are primarily reported in basic research, with limited clinical application. The relationship between abnormal adult hippocampal neurogenesis and cognitive impairment has garnered widespread attention, and targeting the former may be an important strategy for treating the latter. However, the mechanisms underlying abnormal adult hippocampal neurogenesis remain unclear, and treatments are lacking. This highlights the need for greater focus on translating research findings into clinical practice.

Key Words: aging; Alzheimer's disease; cerebrovascular diseases; cognitive impairment; energy metabolism; hippocampus; immune mechanisms; neurogenesis; pathological states; treatment

Introduction

Adult hippocampal neurogenesis (AHN) is a prominent form of plasticity in the adult brain and is believed to play a critical role in memory formation (Fujikawa et al., 2024; Spicer et al., 2025; Wang et al., 2025). Throughout life, new neurons continuously integrate into the granule cell layer of the dentate gyrus, with their numbers increasing in response to experiences such as learning and exercise (Zanirati et al., 2023). During their immature phase, newborn neurons exhibit greater synaptic plasticity, characterized by a lower threshold for long-term potentiation (LTP) induction and increased LTP amplitude, than mature granule cells. Research indicates that AHN is associated with spatial memory, emotional memory, pattern separation, cognitive flexibility, and emotional regulation (Gómez-Oliva et al., 2024; Ma et al., 2024; Xiao et al., 2025). Conversely, abnormalities in AHN can impair hippocampal function, leading to cognitive dysfunction and memory deficits (Terreros-Roncal et al., 2021).

Abnormal neurogenesis has been observed in various diseases and conditions associated with cognitive dysfunction, such as cerebrovascular diseases, neurodegenerative diseases, and aging (Li et al., 2024; Zhang et al., 2024). It is increasingly recognized that AHN disorders are closely related to cognitive decline in these conditions (Berger et al., 2020). In patients with Alzheimer's disease (AD), cognitive decline and psychiatric symptoms are attributed to damage in the hippocampal structure and the impaired development and integration of newly formed hippocampal neurons (Terreros-Roncal et al., 2021). Pathological changes associated with cerebral small vessel disease (CSVD) include decreased vascular density, reduced neural structure density, synapse loss, and neurodegeneration in the hippocampus (Ping et al., 2019). In mammals, adult neurogenesis declines with physiological aging, which is

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accompanied by cognitive dysfunction (Chen et al., 2023). Furthermore, studies have documented reductions in AHN and associated cognitive dysfunction following anesthesia and surgery (Doi et al., 2021; Li et al., 2023).

Studies aimed at treating AHN disorders have shown promise in alleviating cognitive impairment (Carli et al., 2021; Salta et al., 2023). Despite its potential as a therapeutic target for cognitive impairment, the development of corresponding treatments remains limited. Pharmacological interventions, dietary modifications, and physical therapy are the most commonly reported strategies for targeting AHN. These approaches focus on alleviating neuroinflammation, regulating neurogenesis, and enhancing synaptic plasticity, all of which can lead to significant improvements in cognitive function. However, the research landscape concerning treatments for disorders of AHN is relatively sparse, with even fewer studies progressing to clinical trials (Zavvari et al., 2020; Mendonca et al., 2022). Several factors contribute to this gap, including a lack of comprehensive understanding of the mechanisms governing AHN, challenges in target selection, and the inherent complexity of the neurogenic niche.

This review explores the relationship between disorders of AHN and cognitive impairment while highlighting future research opportunities in this area. It summarizes diseases associated with cognitive impairment due to abnormal AHN, elucidates potential mechanisms underlying these abnormalities, and discusses possible treatments targeting AHN to address cognitive dysfunction. By integrating basic research findings with clinical trial outcomes, this review assesses the potential value of AHN-targeted treatments in mitigating cognitive impairment.

Literature Retrieval Strategy

The PubMed database and the ClinicalTrials.gov website were searched for relevant references and trials, respectively, on May 27th, 2024. The search was performed on one day to avoid frequent updates to the database.

The PubMed database was searched for literature on AHN published between 1985 and 2024 using the following terms: ("adult hippocampal neurogenesis" [MeSH Terms] OR "neurogenesis" [MeSH Terms] OR "adult neurogenesis" [MeSH Terms] OR "neural stem cell" [MeSH Terms] OR "adult born neuron" [MeSH Terms] OR "immature neuron" [MeSH Terms]) AND ("cognitive impairment" [MeSH Terms] OR "cognitive decline" [MeSH Terms] OR "cognitive deficits" [MeSH Terms] OR "cognition" [MeSH Terms] OR "cognitive" [MeSH Terms]). The results were further screened by title and abstract, excluding studies that were not relevant to AHN experiments. A total of 154 references were included in this review, all of which are cited in the reference section.

The search for clinical trials was conducted using 'cognition' in the 'condition or disease' input field and 'neurogenesis' in the 'other terms' dialog box. The inclusion criteria were: 1) clear reports in basic research that demonstrate improvements in AHN; and 2) studies that indicated an endpoint measure (such as brain-derived neurotrophic factor [BDNF]). The exclusion criteria were: 1) studies that did not provide clear evidence of improved AHN; and 2) studies with endpoint indicators unrelated to BDNF that did not reflect improvements in AHN. A total of 27 clinical trials were identified, of which 24 were selected for analysis. Authors YL and XD downloaded all references and trials as .tsv files, which were then reviewed by authors SJ and XG to confirm their relevance to the current topic.

Cognitive Dysfunction–Related Conditions With Abnormal Adult Hippocampal Neurogenesis

Cognitive impairment associated with abnormal AHN encompasses a spectrum of conditions, including cerebrovascular diseases, AD, natural aging, and cognitive decline following anesthesia and surgery. **Figure 1** summarizes these conditions. The following sections will provide an in-depth discussion of each of these topics.

Cerebrovascular diseases

Vascular cognitive impairment

Vascular cognitive impairment (VCI) is a syndrome that can be either clinical or subclinical and results from cerebrovascular diseases and associated risk factors (Zhou et al., 2022). Reports indicate that both acute and chronic cerebral hypoperfusion are linked to cognitive impairment and abnormal AHN (Tucsek et al., 2017; Kennedy et al., 2022).

In the context of acute cerebral ischemia, increasing evidence shows that cortical and subcortical infarctions in patients with ischemic stroke disrupt the hippocampal network's integrity, adversely affecting normal hippocampal neurogenesis (Niv et al., 2012; Woitke et al., 2017). Because the hippocampal region is crucial for learning and memory consolidation, the risk of dementia significantly increases in the post-stroke population (Jokinen et al., 2015). Paralysis, motor disorders, sensory deficits, and/or aphasia during the early recovery period are also often associated with cognitive impairment resulting from stroke (Jokinen et al., 2015).

Torres-Lopez et al. (2023) demonstrated that while neurogenesis increased in the early stages of stroke, the newborn neurons exhibited abnormal morphology, displaying different dendritic branching patterns in the ipsilateral and contralateral ischemic brain regions. In the ischemic group, newborn neurons in the ipsilateral hemisphere showed a higher proportion of abnormal features, such as ectopic locations, atypical growth directions, apical bipolar dendrites, and variations in dendritic length compared with the control group. These abnormalities may be linked to elevated gamma-aminobutyric acid levels in the ipsilateral hippocampus following the stroke. Eliminating abnormal neurogenesis in the hippocampus was shown to ameliorate stroke-associated cognitive impairment (Torres-Lopez et al., 2023).

Kathner-Schaffert et al. (2019) induced stroke in 3-month-old mice and investigated the effects across ages 6, 7.5, 9, and 20 months. They found that neurogenesis declined in the 7.5-month-old and 9-month-old groups compared to the sham group. There was also a significant reduction in neurogenesis in stroke animals when comparing the 9-month-old and 20-month-old groups (Walter et al., 2011; Encinas et al., 2012). Furthermore, enhancing hippocampal neurogenesis using physical exercise or pharmacological interventions post-stroke can inadvertently weaken existing memory capacity. This cognitive impairment is at least partly attributable to the pathological remodeling of hippocampal circuits, which is induced by the neurogenic response following a stroke (Cuartero et al., 2019). In summary, during acute cerebral ischemia, there is an initial increase in the generation of new neurons; however, these neurons exhibit morphological and functional abnormalities. As the disease progresses, the number of newborn neurons decreases, leading to the weakening of memory capacity and contributing to post-stroke cognitive impairment.

Chronic cerebral hypoperfusion is associated with cognitive dysfunction and abnormal AHN. Hippocampal neuronal death, glial cell

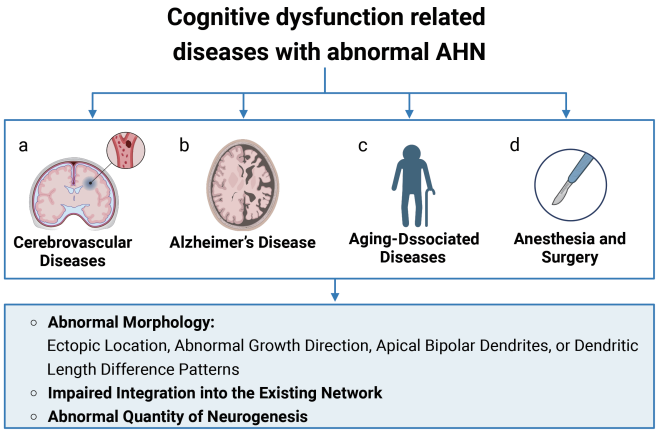

Figure 1 | Cognitive impairment related to abnormal AHN.
Cognitive impairment–related diseases associated with abnormal AHN include: (a) cerebral small vessel disease, (b) Alzheimer's disease, (c) age-related diseases, and (d) anesthesia and surgery. The phenotypic characteristics of abnormal AHN in these conditions typically manifest as: (1) abnormal morphology, including ectopic location, abnormal growth direction, apical bipolar dendrites, or differences in dendritic length patterns; (2) impaired Integration into the existing neural network; and (3) abnormal quantity of neurogenesis. Created with the BioRender.com (ID: UP27F61L06). AHN: Adult hippocampal neurogenesis.

proliferation, and decreased neurogenesis have been observed in the middle and late stages of this condition (Kim et al., 2017; Sun et al., 2022). To explore the relationship between VCI and AHN, Liang et al. (2022) investigated miRNA-140-5p, a molecule involved in axonal growth and neurogenesis. They found that high expression levels of miR-140-5p correlated with an increased risk and severity of depression 3 months post-cerebral infarction. miR-140-5p may inhibit endogenous neurogenesis and neural plasticity in the hippocampal region of mice with cerebral ischemia by targeting Prox1, thereby exacerbating cognitive impairment. This suggests that miR-140-5p could serve as a potential therapeutic target for modulating hippocampal neurogenesis following cerebral ischemia. Additionally, Ping et al. (2019) used a CADASIL transgenic mouse model (TgNotch3R90C)—which simulates CSVD due to a NOTCH3 gene mutation—to demonstrate that the cognitive impairment observed in these mice was linked to decreased vascular density, reduced neural structure density, synapse loss, and diminished neurogenesis—changes attributed to lower levels of VEGF/VEGF-A in brain tissue. Treatment with stem cell factor and granulocyte colony-stimulating factor (SCF + G-CSF) enhanced cognitive function and promoted the regeneration of neuronal structures, synapse formation, and neurogenesis (Ping et al., 2019). In aged animals, Ahn et al. (2016) confirmed reduced neurogenesis in the hippocampal region of VCI mice using a transient cerebral ischemia model. Their study showed that therapeutic physical exercise restored hippocampal neurons and improved memory in aged mice, highlighting the potential of restorative exercise to aid neurogenesis and cognitive recovery. Clinically, an imaging study of the hippocampal region in patients with amnestic VCI revealed significant ultrastructural damage and atrophy, indicating impaired neurogenesis (Hosseini et al., 2017). In summary, during chronic cerebral hypoperfusion, AHN does not follow the pattern seen in acute stroke, where an initial increase is followed by a decrease; instead, it remains in a state of continuous decline. This persistent alteration could contribute significantly to the cognitive decline observed in VCI.

Alzheimer's disease

AD is closely associated with abnormalities in AHN (Zhou et al., 2023). Several mouse models of AD have demonstrated impaired adult neurogenesis in the hippocampus, where newly proliferated granule neurons fail to integrate into the existing neural network, resulting in spatial memory deficits (Richetin et al., 2015; Kim et al., 2022). Hollands et al. (2017) conditionally ablated neurogenesis in APPSWE/PS1ΔE9 mice to investigate whether impaired hippocampal neurogenesis contributes to cognitive decline in AD patients, discovering that the absence of adult neurogenesis impaired performance in fear memory reflex tasks. In the APPSWE/PS1ΔE9 mouse model, cognitive impairment typically manifests around 6 months of age; however, reduced neurogenesis accelerates this process, leading to cognitive deficits as early as 4 months. Furthermore, Richetin et al. (2017) found that decreased mitochondrial biomass in the AD brain disrupted the morphological development and integration of adult-born hippocampal neurons, contributing to cognitive impairment. Utilizing genome editing, they selectively introduced the basic helix-loop-helix transcription factor Neurod1 into the hippocampal neural stem cells of adult rats *in vivo*. This intervention promoted differentiation into neurons and facilitated their integration into the hippocampal circuit while also enhancing mitochondrial content and respiratory function, increasing mitochondria-dendritic spine connections, and improving cognitive abilities (Richetin et al., 2017). Thus, during the progression of AD, adult hippocampal neurogenesis is compromised, which further exacerbates the cognitive impairment symptoms associated with the disease.

Aging-associated diseases

Aging significantly contributes to declining AHN (Ni et al., 2021). Research indicates that AHN decreases with physiological age; this reduction is accompanied by cognitive impairment (Kempermann et al., 1997; Babcock et al., 2021). Studies have confirmed that neurogenesis begins to decline around 6 months of age in mice, coinciding with a deterioration in cognitive and sensory functions (Kempermann et al., 1997; Drapeau et al., 2003; Babcock et al., 2021). Catlin et al. (2021) found that the absence of *Nrmt1*, a critical gene involved in development and aging, enhances the cell cycle phosphorylation of retinoblastoma and promotes the release of E2F1. This results in the premature activation of neurogenic stem cell (NSC) proliferation and neuronal apoptosis. The depletion of the NSC niche, along with high rates of neuronal apoptosis, prevents the replacement of aged or damaged neurons, leading to neurodegeneration and associated behavioral changes (Catlin et al., 2021). Additionally, Qiao et al. (2020) explored the role of microRNA-153 (miR-153) in aged mice, showing that the reduced expression of this microRNA in the hippocampus impaired cognitive ability by affecting neurogenesis via regulation of the Notch signaling pathway. Notably, aging-associated deficits in AHN and spatial memory can also be mitigated by inhibiting glycogen synthase kinase-3β (Liu et al., 2020). We propose that the decrease in neurogenesis seen with aging is primarily caused by the depletion of the neurogenic niche and the upregulation of aging-related genes. This, in turn, contributes to the onset of age-related cognitive decline.

Anesthesia and surgery

Anesthesia- and surgery-induced cognitive impairment has been linked to abnormalities in AHN. Cognitive decline is a common neurological complication following anesthesia and surgery, impacting higher brain functions such as memory, attention, and information processing (Feng et al., 2024). To investigate the relationship between this complication and abnormal AHN, Li et al. (2023) conducted laparoscopic surgery and partial hepatectomy on adult mice, assessing cognitive function and postoperative changes in AHN at 2, 3, and 4 weeks post-procedure. The study found that administering anti-CD8 monoclonal antibodies and IFN-γ neutralizing antibodies resulted in postoperative $CD8^+$ T cell infiltration into the hippocampus, leading to subsequent IFN-γ secretion. This process inhibited AHN and contributed to cognitive decline following surgery. Additionally, Doi et al. (2021) investigated the effects of early anesthesia exposure on subsequent learning impairments. They exposed neonatal mice to midazolam, a commonly used pediatric anesthetic, finding that early exposure to anesthesia resulted in a transient increase in Egr1 expression, which altered chromatin accessibility and affected the expression of quiescence-related genes in hippocampal NSCs. These changes led to a sustained limitation of NSC proliferation in adulthood, resulting in decreased neurogenesis and impaired hippocampus-dependent memory function. In summary, AHN appears to be reduced following anesthesia and surgery, potentially due to an inflammatory response. However, further research is needed to explore the detailed mechanisms underlying this abnormal AHN phenotype.

Potential Mechanisms Underlying Abnormal Adult Hippocampal Neurogenesis

We grouped the potential mechanisms of abnormal AHN into four categories: immunity, energy metabolism, aging, and pathological changes (**Figure 2**). The subsequent sections describe these categories in further detail (**Table 1**).

Adult hippocampal neurogenesis and immunity

The immune system's stability is intimately linked to AHN and cognitive function. Three features, including meningeal immunity, brain immunity, and peripheral immunity, are discussed below.

Meningeal immunity

As a key regulator of central nervous system function, the meninges manage cerebrospinal fluid dynamics and host numerous immune interactions that influence neuronal function. Additionally, the meninges play a crucial role in regulating neural regeneration within the central nervous system (Decimo et al., 2021). They retain bromodeoxyuridine (BrdU) for extended periods, preserving both quiescent and proliferating cells, as well as neural differentiation precursors (Zorzin et al., 2021). For long-term maintenance, stem cells must migrate and establish themselves in a supportive growth environment (Ho et al., 2023). These processes are guided by the recognition of and interaction with chemotactic factors (Kokovay et al., 2010) and tissue-specific extracellular structures (Llorente et al., 2022). Throughout development and into adulthood, meningeal cells express the chemotactic factor stromal cell-derived factor 1 (SDF1/CXCL12) and its receptor, CXC chemokine receptor 4 (CXCR4) (Belmadani et al., 2015). SDF1 is crucial for the homing, migration, proliferation, and differentiation of various stem cell types within their niches. In disease states, cerebral ischemia increases the expression of doublecortin (DCX)-positive cells in the meninges; these cells migrate to the cortex after a stroke, potentially aiding in cortical regeneration and repair (Nakagomi et al., 2012). In the context of bacterial meningitis, meningeal dysfunction and local central nervous system inflammation have been shown to inhibit adult hippocampal neurogenesis (AHN), reduce dentate

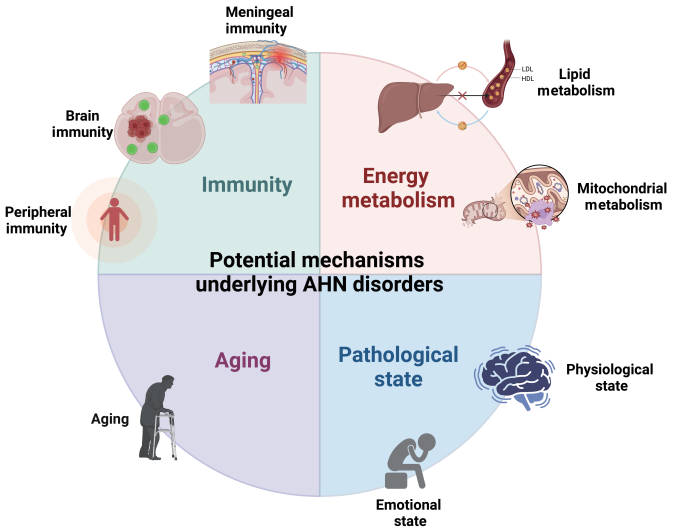

Figure 2 | **The potential mechanisms of abnormal AHN.**
The potential mechanisms underlying abnormal AHN can be categorized into four main aspects: immune function, energy metabolism, aging, and pathological states. In the figure, the green areas represent immune dysfunction, which includes meningeal immune imbalance, brain immune imbalance, and peripheral immune imbalance. The pink areas denote disruptions in energy metabolism, encompassing lipid metabolism imbalances and mitochondrial metabolic disorders. The purple areas illustrate the effects of aging, while the blue areas represent pathological states, such as physical pathologies (e.g., epilepsy) and emotional pathologies (e.g., depression). Created with the BioRender.com (ID: KZ27F61EL0). AHN: Adult hippocampal neurogenesis; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

gyrus volume, and cause cognitive dysfunction in experimental animal models (Hoffmann et al., 2007). Hoffmann et al. (2007) observed a decrease in BrdU-positive cells, the presence of activated iNOS-positive microglia, and increased nitric oxide (NO) production 3 days after meningitis induction (Hoffmann et al., 2007). This neuroinflammatory response following meningitis led to the inhibition of AHN, a reduction in dentate gyrus volume, and subsequent cognitive impairment.

Brain immunity

The role of neuroinflammation in cognitive dysfunction has been widely discussed in recent years. Microglia, the resident immune cells of the central nervous system, are derived from myeloid lineage and resemble macrophages. Microglia become activated upon detecting environmental disturbances and transition into various states to eradicate antigens and/or provide neuroprotection (Loh et al., 2024). While short-term activation of microglia can be beneficial, prolonged activation may induce cellular stress, harm neural tissue health, and lead to neuronal damage, neurodegeneration, and, ultimately, cognitive or motor dysfunction (Winter et al., 2020).

Twenty years ago, Ekdahl et al. (2003) found a significant negative correlation between the number of endotoxin-activated microglia and the generation of new neurons in the hippocampal neurogenic niche. To further investigate the role of microglia in neuroinflammation and the regulation of neurogenesis, Sanchez-Molina et al. (2022) constructed transgenic mice with chronic overexpression of interleukin-10 (IL-10). They found that adult transgenic mice overexpressing this anti-inflammatory cytokine exhibited reduced hippocampal neurogenesis compared to wild-type (WT) mice. T-maze and Morris water maze experiments revealed that excessive IL-10 impaired hippocampal-dependent spatial learning and memory, consistent with reduced neuron formation. The important role that Th1-type cytokine interferon-γ plays in the early immunological response to viral and tumor insults has also been recognized. Zhang et al. (2020) injected interferon-γ into the lateral ventricle of mice and discovered that interferon-γ-activated microglia impaired AHN through the JAK/STAT1 pathway, leading to depressive-like behavior and cognitive impairment. Administering either Ruxolitinib intraperitoneally to inhibit the JAK/STAT1 pathway or minocycline to inhibit microglial activation significantly improved the behavioral phenotype. These findings suggest that regulating interferon-γ levels and targeting microglia may be potential strategies for treating neurodegenerative diseases and mental disorders. In summary, research exploring the relationship between AHN and brain immunity has primarily focused on the interplay between central nervous system inflammation and neurogenesis, with a particular emphasis on the inflammatory state of microglia. However, by considering other types of immune cells, researchers may uncover innovative new mechanisms that contribute to these processes.

Peripheral immunity

In addition to activated microglia, a systemic inflammatory state is also thought to affect cognitive function and adult neurogenesis. The impact of gut ecology on cognitive function has become a hot topic. Studies have revealed a connection between intestinal inflammation and alterations in brain function (Zonis et al., 2015; Olson et al., 2021; Wang et al., 2024). Inflammatory bowel disease, which comprises chronic intestinal inflammatory conditions, is often associated with cognitive impairment and depression. Zonis et al. (2015) used a mouse model of inflammatory bowel disease to demonstrate that pro-inflammatory cytokines, expressed in both the periphery and the hippocampus, inhibited neural precursor cell proliferation by activating the cell cycle CDK inhibitor p21Cip1 in the subgranular zone. This led to decreased AHN and cognitive impairment (Zonis et al., 2015). Changes in the intestinal microbiota also increase susceptibility to cognitive impairment. Using intermittent hypoxia and a ketogenic diet, Olson et al. (2021) altered the gut microbiota, finding that its specific responses to dietary and hypoxic stress might disrupt AHN function and cognitive behavior by inducing pro-inflammatory immune cells. Additionally, Yin et al. (2020) observed a relationship between hippocampal neurogenesis damage and cognitive impairment in sepsis-related encephalopathy. Beyond the pathological processes of systemic inflammation, it is increasingly recognized that age-related and stress-related inflammatory insults significantly impact cognitive abilities (Subeta et al., 2021). The pro-inflammatory cytokine IL-1β is a primary mediator of neuroinflammation, and its receptor is highly expressed in the hippocampus (Ban et al., 1991; Parnet et al., 1994). Under neurodegenerative disease-related inflammatory conditions, IL-1β negatively impacts memory processes. Using a lentivirus method, Hueston et al. (2018) induced prolonged overexpression of IL-1β in the dorsal hippocampus of adult male Sprague–Dawley (SD) rats. They observed a reduction in the number and axonal complexity of immature hippocampal neurons, as well as impaired synaptic integration and cognitive decline in pattern separation tasks in SD rats. Research has also shown that anti-inflammatory drugs can restore neurogenesis following endotoxin-induced inflammation and boost neurogenesis after cranial irradiation (Zisiadis et al., 2023). In summary, peripheral inflammation is one of the factors affecting abnormal adult hippocampal neurogenesis, which is an important mechanism of cognitive impairment.

Adult hippocampal neurogenesis and energy metabolism

Energy metabolism can dynamically and precisely regulate neurogenesis. Several circulating factors play roles in both metabolism and AHN, such as liver-derived insulin-like growth factor-1 (Herrero-Labrador et al., 2023), ghrelin from the stomach (Kraemer et al., 2023), leptin from fat (Garza et al., 2008), and irisin from skeletal muscle (Lourenco et al., 2019). Epidemiological studies highlight a significant link between metabolic disorders, cognitive impairment, and neurodegenerative diseases (Kandimalla et al., 2017; Giuffre et al., 2024). Quiescent NSCs primarily depend on glycolysis and fatty acid oxidation, whereas active NSCs are characterized by enhanced mitochondrial oxidative phosphorylation and lipogenesis. Thus, lipid metabolism and mitochondrial function are essential for the differentiation and survival of NSCs.

Lipid metabolism

Epidemiological studies have confirmed a strong link between metabolic diseases, such as obesity and diabetes, and neurodegenerative disorders (Kandimalla et al., 2017; Giuffre et al., 2024). Furthermore, numerous studies utilizing genetic rodent models of high-fat diets, leptin deficiency,

Table 1 | **Potential mechanisms underlying abnormal adult hippocampal neurogenesis**

Mechanism		Description	Reference
Immunity	Meningeal immunity	(1) The expression of doublecortin-positive cells in the meninges induced by cerebral ischemia increases, and these cells migrate to the cortex after a stroke, potentially contributing to cortical regeneration/repair. (2) In bacterial meningitis, there is a decrease in bromodeoxyuridine-positive cells, the presence of activated inducible nitric oxide synthase–positive microglia, and an increase in local nitric oxide production. The effects of neuroinflammation lead to the inhibition of adult hippocampal neurogenesis and cognitive dysfunction following meningitis.	Hoffmann et al., 2007; Nakagomi et al., 2012
	Brain immunity	(1) There is a significant negative correlation between the number of endotoxin-activated microglia and the number of newborn neurons in the hippocampal neurogenic niche. (2) Excessive production of interleukin-10 impairs hippocampus-dependent spatial learning and memory, which is consistent with the observed reduction in neurogenesis. (3) Interferon-γ-activated microglia impair adult hippocampal neurogenesis through the JAK/STAT1 pathway, leading to depression-like behaviors and cognitive impairment.	Ekdahl et al., 2003; Zhang et al., 2020; Sanchez-Molina et al., 2022
	Peripheral immunity	(1) Pro-inflammatory cytokines expressed in the periphery and hippocampal region inhibit the proliferation of neural precursor cells by activating the cyclin-dependent kinase inhibitor p21Cip1 in the subgranular zone, leading to reduced hippocampal neurogenesis and cognitive impairment. (2) A specific diet and hypoxic stress responses in the gut microbiota may disrupt hippocampal neurogenesis and cognitive behavior by inducing pro-inflammatory immune cells. (3) Hippocampal neurogenesis impairment and cognitive impairment are observed in sepsis-associated encephalopathy. (4) Anti-inflammatory drugs can restore neurogenesis after endotoxin-induced inflammation and enhance neurogenesis following cranial irradiation.	Zonis et al., 2015; Yin et al., 2020; Olson et al., 2021; Zisiadis et al., 2023
Energy metabolism	Lipid metabolism	(1) A high-fat diet with 42% of energy from fat over 4 weeks inhibits hippocampal neurogenesis in rats. This inhibition is gender-related but not associated with obesity. (2) In mice fed a high-fat diet providing 60% of energy from fat, there is a reduction in cell proliferation and differentiation in the dentate gyrus. This effect is believed to be mediated by glucocorticoid dysfunction, as the impairment is reversed when circulating corticosterone levels are elevated.	Lindqvist et al., 2006; Hwang et al., 2008; Yon et al., 2013
	Mitochondrial metabolism	(1) During the development of stem cells into adulthood, newborn neurons undergo extensive changes in mitochondrial biomass, distribution, and morphology. At the morphological level, the mitochondria in hippocampal radial glia-like neural stem cells exhibit a mixture of spherical and tubular shapes, whereas in mature hippocampal neurons, they present a broader and highly elongated morphology. (2) In a genetic Parkinson's disease mouse model, there are mitochondrial defects associated with impaired differentiation of hippocampal dentate gyrus neural stem cells into neuroblasts, as well as mitochondrial defects related to the reduced maturity of newborn neurons. (3) Mitochondrial biogenesis and functional impairments in adult-born neurons of the hippocampus in Alzheimer's disease mice are rescued following Neurod1 overexpression.	Richetin et al., 2015; Agnihotri et al., 2017; Beckervordersandforth et al., 2017
Aging	Aging	(1) In transgenic mice with chronic interleukin-10 overexpression, hippocampal neurogenesis is reduced, and cognitive function declines. These changes observed in adult transgenic animals are similar to the effects of normal aging. (2) In exploring the effects of age-related inflammatory insults on cognitive abilities, chronic overexpression of the pro-inflammatory cytokine interleukin-1β in the hippocampus leads to a reduction in the number of immature neurons and axonal complexity, ultimately resulting in impaired synaptic integration. (3) The brain aging-related microRNA miR-153 mediates hippocampal neurogenesis impairment by specifically modifying the Notch signaling pathway.	Hueston et al., 2018; Qiao et al., 2020; Saraiva et al., 2020
Pathological conditions	Pathophysiological conditions	(1) In Parkinson's disease, the overexpression of α-synuclein reduces neurogenesis in adult-born dentate gyrus cells and impairs their morphological maturation. (2) In a transgenic mouse model of Parkinson's disease, the hippocampus shows high expression of leucine-rich repeat kinase 2, with defects in the proliferation/morphogenesis and survival of newborn neurons. (3) The accumulation of amyloid precursor protein and tau leads to the loss of synapses and neurons, resulting in inhibited adult hippocampal neurogenesis and neuronal maturation in patients with Alzheimer's disease. (4) Seizures damage and deplete adult neural stem cells, significantly increasing abnormal neurogenesis in rodent models and human subjects.	Jessberger et al., 2005; Boekhoorn et al., 2006; Parent et al., 2006; Crews et al., 2010; Winner et al., 2012
	Emotional conditions	(1) Chronic stress can reduce cell proliferation and the survival of newborn neurons in the dentate gyrus. (2) Long-term sleep restriction or sleep fragmentation inhibits the production of new neurons in the dentate gyrus. (3) In rodents, genetic manipulation or endotoxin injection to activate brain inflammation induces depressive, anxious, and schizophrenic behavioral phenotypes while inhibiting the proliferation and survival of new neurons in the dentate gyrus.	Mirescu et al., 2006; Czeh et al., 2007; Dagyte et al., 2009; Schoenfeld et al., 2015

or other metabolic conditions have demonstrated age-related cognitive disorders and accelerated impairment in AHN (Lindqvist et al., 2006; Hwang et al., 2008; Knobloch et al., 2013; Yon et al., 2013). For example, mice with NSC-specific fatty acid synthase exhibited disorders in fat generation that promoted NSC quiescence and impaired AHN (Knobloch et al., 2013). Lindqvist et al. (2006) discovered that a 4-week high-fat diet (comprising 42% of energy from fat) inhibited hippocampal neurogenesis in rats. This effect was gender-related but independent of obesity, as male rats increased fat mass without overall weight gain; however, neurogenesis decreased by nearly 50% (Lindqvist et al., 2006; Yon et al., 2013). In mice consuming a diet with 60% of its energy from fat, comparable strain-related outcomes were observed, persisting for 4 or 12 weeks (Hwang et al., 2008). C57BL/6N mice are more prone to high-fat diet-induced obesity than C3H/HeN mice, showing a greater weight increase, which is related to a decrease in cell proliferation and differentiation in the dentate gyrus. Hippocampal neurogenesis is compromised in rodent models of type 1 and type 2 diabetes (Lu et al., 2021), likely due to glucocorticoid dysfunction. This impairment reverses when circulating corticosterone levels increase (Stranahan et al., 2008; Guo et al., 2010). When investigating the link between insulin resistance and neurodegenerative diseases, AD is often referred to as "type 3 diabetes" (Landry et al., 2021). Thus, impaired lipid metabolism is a key factor contributing to the disruption of AHN and the development of cognitive impairment. Targeting lipid metabolism-related factors through treatment may help restore neurogenesis and improve cognitive function.

Mitochondrial metabolism

The mitochondrial function of NSCs is crucial for their differentiation and survival (Campbell et al., 2023). In mice, the transformation of stem cells into adult-born neurons involves significant alterations in mitochondrial biomass, distribution, and morphology (Beckervordersandforth et al.,

2017; Angelopoulos et al., 2022). Morphologically, the mitochondria of hippocampal radial glial-like NSCs exhibit both spherical and tubular shapes, whereas mature hippocampal neurons display a broader and more extended mitochondrial morphology (Beckervordersandforth et al., 2017). A study on a genetic mouse model of Parkinson's disease (PD) lacking PINK1 identified mitochondrial defects that impaired the differentiation of hippocampal dentate gyrus NSCs into neuroblasts and reduced the maturity of newborn neurons (Agnihotri et al., 2017). There have been reports of severe impairment of adult hippocampal neurogenesis in both patients with AD (Lee et al., 2023; Scaduto et al., 2023) and in mouse models of the disease (Farioli-Vecchioli et al., 2022; Piccialli et al., 2022). In AD mouse models, changes in synapse formation and the connections of new neurons appear to be the cause of memory deficits. In a mouse model of AD, overexpressing the proneural transcription factor Neurod1 into dividing NSCs can restore the morphological development and synaptic integration of hippocampal newborn neurons, effectively reversing memory impairment (Richetin et al., 2015). Additionally, overexpression of Neurod1 in AD mice restores mitochondrial biogenesis and function in adult-born hippocampal neurons (Richetin et al., 2017). In summary, mitochondrial function is vital for the proliferation and differentiation of adult hippocampal neurons. When mitochondrial function is impaired in various disease states, it directly disrupts adult hippocampal neurogenesis, leading to cognitive impairment.

Adult hippocampal neurogenesis and aging

Hippocampal neurogenesis is an ongoing process; however, it diminishes with age, significantly impacting patients' learning and memory functions. Recent studies indicate that the inflammatory state of the neurogenic niche microenvironment, exacerbated by aging, is closely linked to the substantial decline in hippocampal neurogenesis, correlating with cognitive impairment (Ekdahl et al., 2003; Saraiva et al., 2020; Sanchez-Molina et al., 2022). Ekdahl et al. (2003) found a significant inverse correlation between endotoxin-activated microglia and the presence of newborn neurons in the hippocampal neurogenic niche. Sanchez-Molina et al. (2022) developed transgenic mice with chronic overexpression of the anti-inflammatory cytokine interleukin-10 (IL-10) in order to explore the role of microglia in regulating age-induced neuroinflammation and neurogenesis. Compared to WT mice, these transgenic animals exhibited reduced hippocampal neurogenesis and cognitive decline during adulthood. These alterations resembled those seen with normal aging. Similarly, chronic overexpression of IL-10 was found to negatively affect hippocampal neurogenesis, reducing the number of DCX^+ cells in the subventricular zone, whereas IL-10 knockout mice displayed increased DCX expression (Saraiva et al., 2020). In addition, age-related inflammatory insults significantly contribute to the development of neurodegenerative diseases and associated cognitive disorders. Hueston et al. (2018) used a lentivirus method to induce prolonged overexpression of the pro-inflammatory cytokine interleukin-1β (IL-1β) in the dorsal hippocampus of adult male SD rats. They found that hippocampal neurogenesis was impaired, as indicated by a reduction in the number and axonal complexity of immature neurons, as well as impaired synaptic integration and cognitive decline in pattern separation tasks (Hueston et al., 2018). In addition to the inflammatory state, Qiao et al. (2020) demonstrated that age-related microRNA-153 mediated hippocampus-dependent learning and memory impairments by specifically modifying the Notch signaling pathway. Exogenous overexpression of miR-153 in the hippocampus of aged mice enhanced neurogenesis and mitigated cognitive decline. Aging is a significant mechanism underlying the decline of AHN, with age-related neuroinflammation and the expression of aging-related genes being critical factors contributing to AHN abnormalities, ultimately leading to cognitive impairment.

Adult hippocampal neurogenesis and pathological conditions

Notably, AHN is regulated by an individual's emotional and pathophysiological conditions. This indicates that the production of adult-born neurons can be modulated in response to environmental signals, potentially allowing for a degree of subplasticity in the reorganization of hippocampal circuits that depend on AHN.

Pathophysiological conditions

Pathophysiological conditions can impair AHN, typically involving abnormal protein accumulation, oxidative stress, and neuronal degeneration. For instance, a decline in adult NSCs has been observed in PD patients, correlating with the accumulation of α-synuclein (Leem et al., 2022). Balanced levels of α-synuclein are essential for the proper regulation of AHN. Overexpression of α-synuclein reduces the neurogenesis of adult-born dentate granule cells and impairs their morphological maturation (Winner et al., 2012). Similarly, transgenic mice carrying the common G2019S mutation in leucine-rich repeat kinase 2 (LRRK2) show elevated LRRK2 expression in the hippocampus, resulting in defects in the proliferation, morphogenesis, and survival of newborn neurons (Winner et al., 2012). In patients with AD, the accumulation of Tau and amyloid precursor protein (APP) begins in the entorhinal cortex and gradually spreads to the cortex and hippocampus (Jiang et al., 2024). The buildup of APP and Tau leads to synapse and neuron loss, inhibiting AHN and neuronal maturation in patients with AD (Boekhoorn et al., 2006; Crews et al., 2010). In rodent models of and human patients with mesial temporal lobe epilepsy, epileptic seizures initially damage and deplete adult NSCs, with a subsequent significant increase in aberrant neurogenesis (Jessberger et al., 2005; Parent et al., 2006). Beyond cell proliferation, the adult neurons generated in response to epileptic seizures exhibit abnormal migration, morphogenesis, and synaptic integration through various signaling pathways, leading to erroneous network connections and impaired cognitive function (Kasahara et al., 2023). Furthermore, cerebral hypoperfusion can trigger mitochondrial dysfunction, oxidative stress, and inflammatory responses (Stanzione et al., 2024), ultimately resulting in abnormal neurogenesis following ischemic stroke and the death of newborn neurons (Huang et al., 2019). Therefore, in pathophysiological conditions, neuronal death, oxidative stress, and the abnormal accumulation of disease-related proteins can significantly impair AHN, leading to cognitive dysfunction.

Emotional conditions

Emotional conditions such as stress, depression, and anxiety can significantly impair AHN. Stress has long been recognized as a factor contributing to the onset of mental disorders (Kessler et al., 1985). Long-term stress in humans can overwhelm the stress response system, increasing the risk of developing both physical and mental diseases (Saltzman et al., 2024). The hippocampus, which plays a crucial role in linking stress to behavior, contains neurons with high levels of glucocorticoid and mineralocorticoid receptors, which are receptors for stress hormones. These receptors provide negative feedback to the stress response, inhibiting the hypothalamic–pituitary–adrenal axis when stress hormone levels rise (Gerlach et al., 1972; Jankord et al., 2008). The impact of stress on adult neurogenesis is multifaceted; however, chronic stress can decrease cell proliferation and the survival of new neurons in the dentate gyrus (Czeh et al., 2007; Dagyte et al., 2009). Extended sleep restriction or fragmentation can also hinder the generation of new neurons in this region (Mirescu et al., 2006). Prolonged sleep deprivation is considered a contributing factor to emotional disorders such as depression and anxiety (Taylor et al., 2005; Kahn-Greene et al., 2007). Animal studies have demonstrated that sleep deprivation increases anxiety-like behavior in mice (Silva et al., 2004; Schoenfeld et al., 2015). A pro-inflammatory state has been linked to mental disorders, including severe depression, anxiety, and schizophrenia (Fan et al., 2007; Dowlati et al., 2010). Inducing brain inflammation in rodents, either genetically or through endotoxin injection, triggers behavioral phenotypes associated with depression, anxiety, and schizophrenia (Wohleb et al., 2011; Takao et al., 2013) while also inhibiting the proliferation and survival of new neurons in the dentate gyrus (Schoenfeld et al., 2015). Thus, stress, chronic stress, and sleep deprivation can induce anxiety and depressive emotions, inhibit the proliferation and survival of hippocampal neurons, impair AHN, and ultimately lead to cognitive impairment.

Current Methods for Improving Neurogenesis

To investigate strategies for treating AHN abnormality and cognitive impairment, we searched for clinical trials (**Table 2**) registered on ClinicalTrials.gov and for relevant animal studies (**Table 3**) in the PubMed database. A total of 27 clinical trials were identified, of which 24 were closely related to AHN; these were selected for in-depth analysis. **Figure 3** illustrates the timeline of treatment methods targeting AHN for cognitive dysfunction. We have categorized the strategies for enhancing neurogenesis into two main types: physical therapy and non-physical therapy.

Physical therapy

The positive impact of exercise on neuronal health has been extensively demonstrated. Research on rodents indicates that exercise can reduce brain inflammation and enhance hippocampal neurogenesis (Hotting et al., 2013; Leiter et al.,

Table 2 | Clinical trials of targeting adult hippocampal neurogenesis in cognitive impairment

No.	NCT number	Status	Study title	Design and study type	First submitted	Enrollment (*n*)
1	NCT01747811	Completed	Effects of bright light therapy in mild traumatic brain injury	Allocation: Randomized Interventional Model: Parallel Assignment Masking: Double (Participant Outcomes Assessor) Primary Purpose: Treatment	2012/12/6	32
2	NCT02063646	Completed	Effect of a polyphenol-rich food supplement on cognitive function in healthy aging adults	Allocation: Randomized Interventional Model: Parallel Assignment Masking: Quadruple (Participant Care Provider Investigator Outcomes Assessor) Primary Purpose: Prevention	2014/2/12	204
3	NCT02151266	Completed	Exercise and cognitive retraining to improve cognition in heart failure	Allocation: Randomized Interventional Model: Parallel Assignment Masking: Single (Outcomes Assessor) Primary Purpose: Supportive Care	2014/5/28	69
4	NCT02525198	Completed	The cognitive ageing nutrition and neurogenesis (CANN) trial	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, investigator, outcomes assessor) Primary Purpose: Treatment	2015/5/11	259
5	NCT02957123	Completed	Intranasal inhalations of bioactive factors produced by M2 macrophages in patients with organic brain syndrome	Allocation: N/A Interventional Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	2016/11/3	30
6	NCT02985580	Completed	Effects of blueberry juice consumption on cognitive function in healthy older people	Allocation: Randomized Interventional Model: Parallel Assignment Masking: Triple (Participant Investigator Outcomes Assessor) Primary Purpose: Basic Science	2016/9/13	26
7	NCT03036371	Completed	Pilot study of the impact of exercise on hippocampal function	Allocation: N/A Interventional Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	2017/1/3	14
8	NCT03696082	Terminated	A precision rehabilitation approach to counteract age-related cognitive declines	Allocation: Randomized Interventional Model: Sequential Assignment Masking: Single (Outcomes Assessor) Primary Purpose: Other	2018/9/13	78
9	NCT03478527	Completed	Probiotics, brain structure and psychological variables	Allocation: Randomized Interventional Model: Parallel Assignment Masking: Double (Participant Investigator) Primary Purpose: Basic Science	2018/1/26	59
10	NCT03608462	Unknown status	Modulation of repetitive transcranial magnetic stimulation on hippocampal neurogenesis and functional network in patients with schizophrenia	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor) Primary Purpose: Treatment	2018/7/9	180
11	NCT03670615	Recruiting	Using exercise and electrical brain stimulation to improve memory in dementia	Allocation: Randomized Interventional Model: Parallel Assignment Masking: Triple (Participant Investigator Outcomes Assessor) Primary Purpose: Treatment	2018/8/22	60
12	NCT03457870	Completed	Intermittent energy restriction and chewing on neural stem cell ageing and adult hippocampal neurogenesis associated cognition	Allocation: Randomized Interventional Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Prevention	2018/2/23	123
13	NCT04271943	Active, not recruiting	The effect of aerobic and game based exercises on cognitive functions in dementia	Allocation: Randomized Interventional Model: Parallel Assignment Masking: Single (Participant) Primary Purpose: Treatment	2020/2/14	30
14	NCT04390646	Recruiting	GnRH therapy on cognition in down syndrome	Allocation: Randomized Interventional Model: Parallel Assignment Masking: Triple (Participant Care Provider Investigator) Primary Purpose: Treatment	2020/5/5	56
15	NCT04831203	Completed	NWT-03 and brain function	Allocation: Randomized Interventional Model: Parallel Assignment Masking: Double (Participant Investigator)Primary Purpose: Prevention Primary Purpose: Prevention	2021/4/1	44
16	NCT05179083	Recruiting	Exercise for brain regeneration in epilepsy	Allocation: Randomized Interventional Model: Parallel Assignment Masking: Quadruple (Participant Care Provider Investigator Outcomes Assessor) Primary Purpose: Other	2021/11/30	10
17	NCT05397990	Unknown status	The impact of exercise on hippocampus-dependent cognition and the gut microbiota	Allocation: Randomized Interventional Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Basic Science	2022/5/20	120
18	NCT05363228	Recruiting	The effect of Tai Chi and therapy by dance and movement on blood irisin levels in older adults over 65 years of age	Allocation: Randomized Interventional Model: Parallel Assignment Masking: Single (Outcomes Assessor) Primary Purpose: Prevention	2022/5/3	90
19	NCT06081218	Not yet recruiting	Effect of acute exercise on cognitive functions and blood markers of brain plasticity in regular chronic cannabis users	Allocation: Non-Randomized Interventional Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Other	2023/7/6	60

Table 2 | **Continued**

No.	NCT number	Status	Study title	Design and study type	First submitted	Enrollment (*n*)
20	NCT06114550	Not yet recruiting	Resistance training on growth factors	Allocation: Randomized Intervention Model: Crossover Assignment Masking: Triple (Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	2023/10/24	12
21	NCT06143241	Recruiting	Cognitive function and glymphatic system in children with epilepsy	Allocation: Randomized Interventional Model: Parallel Assignment Masking: Double (Participant Outcomes Assessor) Primary Purpose: Treatment	2023/11/16	20
22	NCT05839405	Recruiting	Food allergy in the brain	Observational Model: Cohort Time Perspective: Cross-Sectional	2023/2/27	50
23	NCT05755321	Active, not recruiting	From skin fibroblasts to neural stem cells to investigate *in vitro* the impact of diabetes on adult neurogenesis	Observational Model: Cohort Time Perspective: Prospective	2023/2/23	40
24	NCT05890183	Recruiting	Improving cognition through telehealth aerobic exercise and cognitive training after a first schizophrenia episode	Allocation: Randomized Interventional Model: Parallel Assignment Masking: Single (Outcomes Assessor) Masking Description: An assessor of functional outcome will be blind to treatment condition. Primary Purpose: Treatment	2023/5/9	100

GnRH: A decapeptide secreted by hypothalamic neurons is the pilot light of reproduction in all mammals.

Table 3 | **Current methods of improving adult hippocampal neurogenesis**

Approach		Method	Description	Reference
Physical therapy	Physical therapy	Exercise	Physical activity can activate platelets, leading to the release of platelet factor 4, which promotes AHN and restores cognitive function in the aging brain.	Norevik et al., 2023
		Enriched environments	An enriched environment can improve plasma ApoE levels in a mouse model of Alzheimer's disease and enhance AHN.	Ehret et al., 2023
Non-physical therapy	Dietary therapy	Caloric intake	A reduction in caloric intake by 30%–40% can lead to an increase in the quantity of AHN.	Mattson, 2000; Lee et al., 2002
		Meal frequency	Prolonging the interval between meals can enhance adult neurogenesis in mice, and improve performance in hippocampus-dependent tasks and emotional responses.	Stangl et al., 2009
		Meal texture	Feeding a soft diet can result in a decrease in the proliferation of hippocampal neural stem cells.	Aoki et al., 2005
		DHA treatment	Elderly rats treated with DHA demonstrated enhanced long-term potentiation and synaptic protein expression, as well as increased dendritic spine density and neurogenesis in the hippocampus.	Su, 2010
		Flavonoids	Through the mediation of BDNF, flavonoids increase AHN in rats under chronic stress.	Dimpfel, 2009
		Resveratrol	Resveratrol improves hippocampal atrophy in a chronic fatigue mouse model by enhancing AHN, improving the expression of BDNF in the hippocampus, and inhibiting the expression of neuronal and acetylated r53 in the hippocampus.	Moriya et al., 2011
	Pharmacotherapy	Metformin	Metformin treatment, by regulating the composition of gut microbiota in mice, inhibits neuroinflammation, thereby restoring the damage to neurogenesis in the hippocampal subgranular zone.	Ma et al., 2021
		LINGO-1 antibody	Antagonism of LINGO-1 can effectively prevent the loss of hippocampal neurons and promote adult hippocampal neurogenesis.	He et al., 2013
		SCF + G-CSF	Repeated treatments with SCF and G-CSF in a mouse model of CADASIL promotes the regeneration of neuronal structures, synaptogenesis, and neurogenesis.	Cui et al., 2015
		TGF-α	The use of TGF-α for targeted molecular therapy in SAMP8 mice actively regulates neurogenesis and improves cognitive abilities, offsetting the neurological impacts of pathological aging.	Gomez-Oliva et al., 2023
		PGRN	After permanent middle cerebral artery occlusion surgery, the injection of recombinant mouse PGRN can promote hippocampal neurogenesis, thereby alleviating anxiety-like behavior and spatial learning and memory impairment caused by cerebral ischemia.	Sun et al., 2022
		Fibroblast growth factor-2 and allopregnanolone	Fibroblast growth factor-2 and allopregnanolone can stimulate the proliferation of neural precursor cells in the adult brain, improving hippocampal synaptic plasticity and learning and memory abilities.	Zhao et al., 2007; Wang et al., 2010

AHN: Adult hippocampal neurogenesis; Apo-E: apolipoprotein E; BDNF: brain-derived neurotrophic factor; DHA: docosahexaenoic acid; PGRN: progranulin; SCF + G-CSF: stem cell factor and granulocyte colony-stimulating factor; TGF-α: transforming growth factor-alpha.

2023). To explore the potential benefits of athletes' blood, Norevik et al. (2023) investigated the effects of plasma from exercise-trained donors both *in vitro* and *in vivo*, assessing its role in the HT22 AD neuronal cell culture model and in AD rats. They found that plasma from exercised donors not only increased the survival rate of neuronal cells in the AD model but also boosted hippocampal neurogenesis nearly threefold compared to rats given saline. Another study transfused plasma from young donors into patients with mild cognitive impairment or early AD, and the analysis of the results indicated an improvement in cognitive ability (Sha et al., 2019). Through further research on the beneficial components of plasma, Leiter et al. (2023) discovered that exercise activates platelets and releases humoral factors such as chemokine-platelet factor 4. Systemic injection of platelet factor 4 can mimic the rejuvenating effects of exercise, promoting adult hippocampal neurogenesis and restoring cognitive function in the aging brain (Leiter et al., 2023).

Numerous clinical trials are investigating the positive effects of various forms of exercise on AHN. NCT05890183, currently in the recruitment phase, is a trial investigating the combined effects of cognitive health training and aerobic exercise on cognitive deficits in patients with schizophrenia. The primary target of this study is mature BDNF, with cognitive improvement as the main outcome. The goal is to maximize cognitive enhancement in real-world functional outcomes shortly after the initial onset of schizophrenia before chronic disability develops.

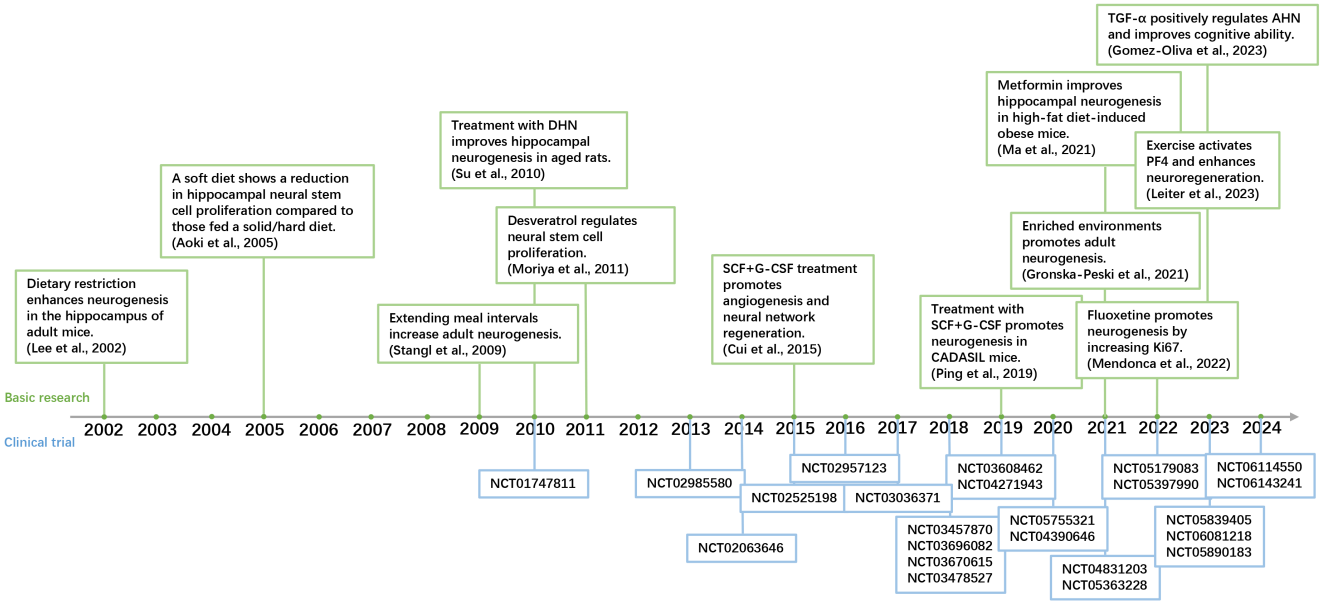

Figure 3 | **Timeline of targeting AHN in treating cognitive impairment.**
This timeline illustrates therapeutic strategies targeting AHN to treat cognitive impairment. Green boxes represent treatment strategies derived from fundamental research, while blue boxes denote clinical trials that can be found on the ClinicalTrials website. AHN: Adult hippocampal neurogenesis; CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; PF4: chemokine-platelet factor 4; SCF + G-CSF: stem cell factor and granulocyte colony-stimulating factor; TGF-α: transforming growth factor-alpha.

NCT03036371 is an initial study investigating whether high-intensity interval training can enhance hippocampal-dependent behavior or alleviate anxiety. Although this study has been completed, its conclusions have not yet been published. NCT02151266 focuses on alleviating cognitive impairment in patients with heart failure. This trial evaluates the acceptability and limited efficacy of a combined exercise and cognitive training program in improving cognitive deficits in patients with stable NYHA Class II and III heart failure, compared to a control group receiving only exercise or no intervention. The results indicated that the combined intervention of exercise and cognitive training significantly improved cognitive function, quality of life, and physiological markers of brain function in patients with heart failure (Gary et al., 2019).

NCT05397990 is a study on exercise, hippocampal neurogenesis, and the gut microbiome in middle-aged populations. It explores how exercise alters the gut microbiome and its metabolites in middle-aged adults, aiming to develop and test a group-based exercise intervention to identify specific gut microbiota and metabolic markers that influence cognitive and emotional changes. However, the current status of this study is unknown.

Transcranial direct current stimulation and improved sleep quality can also enhance AHN and cognitive function. NCT03608462 investigates whether high-frequency repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex and left parietal cortex in patients with schizophrenia can normalize cognitive abnormalities by enhancing hippocampal neurogenesis and cortical hippocampal function. This study aims to utilize multimodal functional magnetic resonance imaging (fMRI) methods (including structural MRI, resting-state fMRI, and 1H-MRS) to assess the therapeutic effects of intermittent theta burst stimulation on cognitive impairment in patients with memory deficiencies, as well as to elucidate the correlation between these effects and hippocampal neuroplasticity. The current status of this study is unknown. NCT03670615, currently in the recruitment phase, seeks to combine exercise with transcranial direct current stimulation that targets important brain regions to determine whether this approach can improve memory in patients with mild cognitive impairment or AD. To investigate the effects of sleep quality on AHN, NCT01747811 used bright light therapy, a particularly promising non-pharmacological method. This therapy demonstrates the potential to improve abnormalities in circadian rhythms and sleep-wake schedules. The study, which has now concluded, found that bright light therapy enhances sleep in patients who have recently experienced a mild traumatic brain injury, increases the likelihood of quicker recovery, and fosters emotional and cognitive resilience.

Enriched environments (EEs) are considered beneficial for AHN. EEs serve as a crucial experimental model for understanding how gene–environment interactions reshape brain structure and function throughout an animal's lifespan. Current research has shown that EEs can influence gene expression in various cells and tissues, alter protein production, and regulate biochemical processes, including neurotransmitters, neurotrophic factors, hormones, and immune factors (Kempermann, 2019). In the context of chronic disease treatment, EEs can improve disease phenotypes and enhance recovery capabilities. They remain effective throughout life, even into old age. The enhancement of neurogenesis and cognitive function through EEs has been documented in numerous studies. For instance, Ehret et al. (2023) found that 4 months of an EE increased plasma ApoE levels in a mouse model of AD and increased AHN. Furthermore, even after discontinuing the EE, the plasticity of mouse brain cells exhibited lasting effects (Ehret et al., 2023). Grońska-Pęski et al. (2021) found that EE can autonomously enhance fibroblast growth factor receptor function in neurogenic cells, stimulate stem cell proliferation, boost adult neurogenesis, and improve cognitive function. Additionally, Wang et al. (2022) reported that EEs could reverse the effects of prenatal exposure to halothane on offspring's learning and memory by increasing hippocampal stem cell proliferation. EE is a widely studied behavioral paradigm, transcending the traditional concept of environmental influence on behavior by promoting neurogenesis through the bidirectional regulation of plasticity via behavioral modulation. This simple and effective treatment method is worthy of clinical promotion and represents a positive and impactful approach to enhancing neurogenesis and improving cognitive impairment.

Non-Physical therapy

This review will provide an in-depth discussion of dietary therapy and pharmacotherapy within the scope of non-physical therapies.

Dietary therapy

Diet plays a crucial role in regulating AHN, influencing it through factors such as caloric intake, meal frequency, meal texture, and content (Merlo et al., 2024). Caloric restriction creates an environment that enhances neuroplasticity, improves cognitive function, stimulates AHN, and regulates inflammatory responses (Mayor, 2023). Studies using rodent models have shown that reducing caloric intake by 30%–40% can increase the number of newborn neurons, leading to improved cognitive behavior in models of neurodegenerative diseases (Mattson, 2000; Lee et al., 2002; Park et al., 2011). In addition, research indicates that extending meal intervals—without significantly altering caloric intake—also increases adult neurogenesis in mice and enhances

performance in hippocampus-dependent tasks and emotional regulation (Stangl et al., 2009). In a study investigating the effect of food texture on AHN, Aoki et al. (2005) found that rats on a soft diet exhibited less hippocampal NSC proliferation compared to those on a solid/hard diet. Further investigation revealed that chewing activity is vital for regulating neuronal proliferation; insufficient chewing during development and aging can hinder the proliferation of NSCs in adulthood (Yamamoto et al., 2009).

Various bioactive substances and nutritional components in food can also regulate neurogenesis. Omega-3 polyunsaturated fatty acids (PUFAs), including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are well-known for their significant neuroprotective effects during aging (Kalmijn et al., 1997). Su (2010) found that neurogenesis mediates the effects of DHA on learning and memory. Elderly rats treated with DHA exhibited improved long-term potentiation, enhanced synaptic protein expression, increased dendritic spine density, and greater neuron generation in the hippocampus compared with rats not treated with DHA. Retinol signaling may play a role in mediating the effects of DHA on neurogenesis.

Another widely studied group of nutritional substances is polyphenolic compounds, which include flavonoids found abundantly in foods such as cocoa and blueberries. One study demonstrated that flavonoids may increase AHN in rats subjected to chronic stress, likely mediated by BDNF (Dimpfel, 2009). Other dietary polyphenols, such as resveratrol, have also been shown to regulate NSC proliferation. Moriya et al. (2011) reported that, in a chronic fatigue mouse model, resveratrol enhanced AHN, improved BDNF expression in the hippocampus, and inhibited neuron and acetylated p53 expression, thereby helping to ameliorate hippocampal atrophy. Additionally, Harada et al. (2011) found that resveratrol enhanced cognitive function in mice by increasing hippocampal production of insulin-like growth factor-1, which is stimulated by gastrointestinal sensory neurons.

NCT02525198 is a clinical trial focusing on cognitive aging, nutrition, and neurogenesis. It uses a research product that combines fatty acids and flavonoids to investigate their effects on cognition in older adults with mild cognitive impairment or subjective memory impairment. Utilizing MRI, participants' hippocampal volume is measured, and the CDR Computerized Cognitive Assessment System is used to evaluate the cognitive effects of the treatment. Cerebral blood flow and blood–brain barrier permeability are also assessed. The goal is to identify an effective dietary intervention to prevent or delay cognitive impairment in at-risk individuals, ultimately reducing the overall burden of dementia in the population (Irvine et al., 2018). Clinical trials NCT02985580 and NCT02063646 explore blueberry concentrate and food polyphenols supplementation, respectively, with the aim of enhancing neuronal function (inducing neurogenesis) and maintaining cognitive function in older adults using dietary supplements. Although these three clinical trials have been completed, their conclusions have yet to be published. NCT03457870 is an innovative study examining how periodic prolonged chewing and intermittent energy restriction can enhance cognitive performance. This experiment intends to explore whether intermittent energy restriction and/or prolonged mastication can improve performance on hippocampus-dependent memory tasks and increase levels of the anti-aging marker Klotho in older, overweight participants. While the study has completed the recruitment phase, the results have not yet been published.

Pharmacotherapy

Recent pharmacotherapy studies suggest that inhibiting microglial activation and neuroinflammation can promote neurogenesis and improve cognitive decline. In 2021, a study by Ma et al. on diabetic mice found that metformin enhanced hippocampal neurogenesis and improved learning and memory in high-fat diet-induced obese mice. By regulating gut microbiota composition, metformin inhibited neuroinflammation, restored neurogenesis in the hippocampal subgranular zone, and prevented cognitive decline. Two studies (Zavvari et al., 2020; Mendonca et al., 2022) have demonstrated that fluoxetine, a selective serotonin reuptake inhibitor widely prescribed for anxiety and depression, positively influences hippocampal neurogenesis. In their research on PD treatments, Mendonca et al. (2022) found that a combination of metformin and fluoxetine increased the number of dopaminergic neuron-positive cells while decreasing IBA1 and glial fibrillary acidic protein (GFAP)-positive cell counts in the hippocampus. Fluoxetine also reduced cell death, lowered levels of caspase-3 and IL-1β, and promoted neurogenesis by increasing Ki67. However, one study indicated that fluoxetine may induce significant epileptic-like activity in WT mice (Musaelyan et al., 2024). Researchers should therefore closely examine the treatment mechanisms associated with this drug.

The deposition of amyloid-beta (Aβ) is well recognized as a significant cause of hippocampal neuron loss in AD patients (He et al., 2013). Existing research indicates that LINGO-1 can bind to APP and increase the production of Aβ. LINGO-1 is a nervous system-specific transmembrane protein characterized by leucine-rich repeat and immunoglobulin-like domains. It is expressed in hippocampal neurons, where it negatively regulates neuron survival (Mi et al., 2004). He et al. (2021) demonstrated that antagonizing LINGO-1 prevents hippocampal neuron loss and significantly enhances cognitive abilities. Treating APP/PS1 transgenic AD mice with an anti-LINGO-1 antibody also promotes AHN. Consequently, anti-LINGO-1 antibodies may provide a crucial foundation for developing future AD prevention strategies and treatment drugs.

SCF and G-CSF are vital hematopoietic growth factors. During the chronic phase of experimental stroke, treatment with SCF combined with G-CSF has been shown to enhance angiogenesis, promote neural network regeneration, and improve functional recovery (Cui et al., 2015). A study found that repeated SCF and G-CSF treatment in CADASIL mouse models (autosomal dominant cerebral arteriopathy with subcortical infarcts and leukoencephalopathy) promoted the regeneration of neuronal structures, synaptogenesis, and AHN in mice (Ping et al., 2019). Ping et al. (2019) found that using angiogenesis inhibitors to neutralize vascular endothelial growth factor-A completely abolished SCF- and G-CSF-induced improvements in cognitive function, vascular and neuronal structure regeneration, synaptogenesis, and neurogenesis in CADASIL mice. To investigate the neural effects of brain aging prevention, researchers developed a targeted drug that regulates AHN. Gomez-Oliva et al. (2023) used SAMP8 mice as a model of neuropathological aging and treated them with a transforming growth factor-alpha (TGF-α) targeting molecule, which positively regulated AHN, improved cognitive ability, and counteracted the neural effects of pathological aging.

Progranulin is a secretory glycoprotein known for its effects on cell proliferation across various cell types. Sun et al. (2022) performed permanent middle cerebral artery occlusion surgery on adult male C57BL/6 mice and injected recombinant mouse progranulin intracerebroventricularly 30 minutes after surgery. They found that progranulin enhances AHN by activating the MAPK/ERK and PI3K/Akt signaling pathways, thereby reducing anxiety-like behavior and improving spatial learning and memory impaired by cerebral ischemia. Additionally, fibroblast growth factor-2 and allopregnanolone (APα) have been shown to stimulate the proliferation of neural precursor cells in the adult brain, enhance hippocampal synaptic plasticity, and improve learning and memory abilities. These factors may serve as neurogenesis treatments to prevent or delay mild cognitive impairment (Zhao et al., 2007; Wang et al., 2010).

NCT02957123 is an innovative proof-of-concept trial, the core principle of which is the reparative ability of the central nervous system and the crucial role of macrophages in this process. Type 2 macrophages exhibit anti-inflammatory and reparative potential, primarily through the production of various bioactive factors, which suppress inflammation, protect neurons from apoptosis, stimulate neurogenesis, promote axonal growth and myelin regeneration, form new synapses, and activate angiogenesis. The results of this study demonstrate that cell therapy based on M2 macrophages is safe, effective, and capable of improving cognitive function in patients with organic brain syndrome. NCT03478527 is another trial designed to investigate the intricate relationships between gut microbiota, brain function, brain structure, and the consequent behavioral outcomes, such as cognitive function and mental disorders. This trial involves healthy human participants taking probiotic dietary supplements continuously for 28 days. To explore the effects of probiotics on various cognitive functions, MRI is used to examine structural and functional changes in the hippocampus, along with variations in BDNF and oxytocin. This study particularly focuses on cognitive functions related to hippocampal activity, such as spatial memory and verbal memory, in order to advance research in this field. While this study has completed recruitment, the results have not yet been published.

Limitations

This review has some limitations. First, our literature search was confined to the PubMed

database, which may have led us to overlook relevant studies in other databases, potentially affecting the comprehensiveness and accuracy of our findings. Second, we limited our study to English-language publications, which may result in an underestimation of contributions from non-English sources. Additionally, we only searched for clinical trials on ClinicalTrials.gov, possibly missing relevant trials in other databases. Our search was conducted on May 27, 2024, to avoid the issues associated with frequent database updates. While reasons for trial withdrawal or termination could provide valuable insights for AHN-targeted therapy, such information is not directly available on ClinicalTrials.gov. Factors such as trial design, small sample sizes, failure to meet endpoints, and potential toxic effects may lead to discontinuation of trials in both animal and human studies. Therefore, potential biases in research design must be considered when interpreting the results. Although this article covers multiple aspects of AHN, the depth of each topic may be limited. A substantial amount of research still needs to be explored for each disease, mechanism, and treatment method. Due to the rapid advancement of scientific research, this article may not include the most recent findings. In addition, it may not encompass all diseases and treatment methods related to AHN; for example, some rare neurodegenerative diseases and emerging treatment approaches may be excluded. Lastly, this review's narrow focus on cognitive impairments may mean that other related symptoms that could benefit from AHN-targeted therapies have been overlooked.

Discussion

This review discusses the current understanding and prospects of targeting neurogenesis for the treatment of cognitive impairment, examining conditions closely associated with abnormal AHN, including cerebrovascular diseases, AD, age-related disorders, and the effects of anesthesia and surgery. The review outlines the mechanisms underlying AHN abnormalities, such as immune responses, metabolic status, aging factors, and pathological changes. Furthermore, it explores current therapeutic methods aimed at enhancing cognitive function by targeting AHN. These methods include, but are not limited to, dietary improvements, physical exercise, transcranial electrical stimulation, pharmacological interventions, and stem cell therapy.

The existence of AHN is widely accepted, yet its relationship with cognitive function remains controversial. Using donated human brain samples and animal models, researchers have confirmed AHN in adult mammals, assessing neuronal changes with age, as well as cell turnover and integration. This discovery provides a substantial theoretical foundation for the long-debated question of whether AHN occurs in the brain while also affirming the contribution of adult hippocampal neuron generation to human brain function. However, the role of AHN in cognitive function is still a subject of debate. Scholars have observed AHN abnormalities in various cognitive impairment models. These abnormalities include fewer newborn neurons, abnormal morphology and growth patterns, failure to integrate into the hippocampal spatial network, and other phenotypes (Richetin et al., 2017; Torres-Lopez et al., 2023). The correction of AHN abnormalities has been found to enhance cognitive function, yet the extent to which AHN abnormalities contribute to cognitive impairment remains unclear. Consequently, some scholars argue that while AHN is not a key factor in cognitive impairment, there is a notable correlation. This controversy stems from the current limited understanding of AHN. Although first described in the 1960s, limitations in available tools and difficulties in accurately defining cell phenotypes have hindered a comprehensive understanding of AHN's detailed mechanisms to this day.

With rapid advancements in science and technology, the techniques for detecting AHN have significantly progressed (Just et al., 2022). Immunohistochemistry uses specific antibodies to label markers of new neurons, such as DCX, Nestin, and Ki-67, enabling researchers to efficiently detect and localize the distribution and density of new neurons in tissue sections. Single-cell RNA sequencing (scRNA-seq) technology allows researchers to identify and classify diverse cell types while monitoring gene expression changes in new neurons (Franjic et al., 2022). Radiolabeled markers, such as BrdU and EdU, confirm the presence of new neurons by labeling their DNA and quantifying their generation (Moreno-Jiménez et al., 2021). Additionally, 15N-thymidine, a benign form of thymidine, has been reported to facilitate *in vivo* labeling in adult human patients. Through multi-isotope imaging mass spectrometry, it is possible to track cell renewal in the human brain (Roeder et al., 2023).

Advancements in neuroimaging technology have also provided important tools for AHN research. Diffusion magnetic resonance imaging (dMRI) offers insights into neurogenesis in the hippocampal dentate gyrus cell layer by detecting changes in the diffusion properties of water molecules (Pereira et al., 2007; Pfyffer et al., 2023). Positron emission tomography utilizes radiolabeled tracers to mark specific neurogenesis-related molecules, revealing the presence and distribution of new neurons (Tamura et al., 2017). fMRI infers the dynamic processes of neurogenesis by detecting changes in brain activity (Morozumi et al., 2023). Furthermore, MRI measurements of cerebral blood volume, which leverage the coupling between neurogenesis and angiogenesis, can indirectly provide imaging evidence of neurogenesis (Pereira et al., 2007).

Current research attributes the mechanisms underlying abnormalities in AHN to four main categories: brain immunity, energy metabolism, aging, and pathological states of the brain. The role of neuroinflammation and dysfunctional microglia in the cognitive impairment caused by neurodegenerative diseases and aging is a particularly hot topic. While current studies indicate a close relationship between cognitive impairment, AHN abnormalities, and neuroinflammatory states, several questions remain unanswered. Specifically, how does neuroinflammation mediate AHN abnormalities? What causes the different states of AHN abnormalities in various disease contexts? Furthermore, are there other cell types, aside from microglia, that participate in the mechanisms underlying AHN abnormalities?

Lipid metabolism disorders resulting from high-fat diets and mitochondrial dysfunction are also implicated in AHN abnormalities, which can lead to cognitive decline. Research suggests that individuals with diabetes or obesity have an elevated risk of developing neurodegenerative diseases and experiencing cognitive decline (Kandimalla et al., 2017). However, numerous questions persist regarding the causal links between metabolic diseases and neuronal disorders. For instance, do the weakened functions of neurogenesis-promoting hormones such as insulin, IGF1/2, and leptin contribute to the development of AHN abnormalities, and what specific roles do they play? Is there a relationship between increased cellular damage caused by reactive oxygen species and inflammation? Besides the damage resulting from neuroinflammation, what other potential mechanisms could be involved? These questions warrant further investigation.

In our research on treatment strategies for AHN, we grouped current therapies into two main categories: physical therapy and non-physical therapy. Our review of clinical trials targeting AHN revealed that the primary treatment methods focus on regulating energy metabolism and dietary habits, enhancing exercise, and utilizing pharmacological interventions to reduce neuroinflammation. However, many treatment strategies that have demonstrated efficacy in animal models have yet to be tested in clinical trials. We speculate that the translation of experimental results from mouse models to the human brain presents significant challenges due to species differences, genetic backgrounds, gender, and age. One promising area involves treatments that stimulate NSC proliferation using growth factors. Species differences are a key factor influencing this translation. Mice are often selected for basic experimental research to replicate disease models due to their genetic similarity to humans, cost-effectiveness, and operational flexibility. However, there are substantial physiological and genetic differences between mice and humans. For instance, mice have a faster metabolic rate, distinct hormone levels, and different immune system dynamics compared to humans. In addition, the complex pathological features of neurodegenerative diseases in humans cannot be fully replicated in mouse models. The metabolic pathways for drugs also vary between mice and humans, potentially leading to scenarios where drugs that are effective in mouse models prove ineffective or exhibit different side effects in humans. Even when drugs are effective, converting the dosage from animal models to humans presents significant challenges.

We found that the number of current clinical trials targeting AHN is limited. Among the 24 clinical trials we identified, 10 have been completed, the status of two is unknown, and seven are currently recruiting participants. While basic research uses various techniques, such as immunofluorescence labeling and *in vivo* imaging, to detect the state of neurogenesis, clinical research faces significant limitations in directly detecting and characterizing its degree. Most clinical trials primarily use BDNF

as a quantitative indicator of neurogenesis. For instance, the completed trial NCT03457870 demonstrated that periodic long-term chewing and intermittent energy restriction could significantly enhance AHN and cognitive abilities in mice. This was achieved by labeling proliferating neurons in the hippocampal dentate gyrus with BrdU (Akazawa et al., 2013; Murphy et al., 2014). In human studies, while some authors reported that dietary interventions can improve cognitive function in older adult patients, the methods available for assessing AHN remain restricted to measuring BDNF and cerebral blood flow (Pereira et al., 2007; Witte et al., 2009). We believe that the limitations in detection methods are a significant reason for the relatively few clinical trials currently underway. The development and application of new techniques could have important implications for the diagnosis and treatment of AHN and cognitive function. Ethical issues also warrant careful consideration. Although interventions targeting AHN may offer new avenues for treating cognitive impairment, depression, and other neuropsychiatric disorders, the long-term effects of such interventions are not well understood and could pose unknown risks or side effects. Furthermore, using AHN interventions to enhance cognition in healthy individuals raises ethical concerns, particularly regarding fairness and potential misuse. Ensuring animal welfare and adhering to strict ethical and legal standards when using animal models for research are also significant concerns.

Despite significant advancements in research on and detection of AHN, many mysteries and future research directions remain. Future studies should prioritize exploring new therapeutic targets for AHN, which could aid in developing novel treatments for cognitive disorders. Additionally, creating more sensitive and specific methods for measuring AHN could enable precise monitoring of the dynamic changes in neurogenesis. This is particularly important for human neuroimaging techniques, as improved methodologies could provide valuable insights into various physiological and pathological conditions, ultimately aiding in the diagnosis and treatment of cognitive disorders. In addition, future research should focus on the long-term impacts of interventions on cognitive function. By thoroughly investigating different types of interventions, as well as their timing and intensity, we can better understand the potential of AHN-targeted therapies to prevent or mitigate cognitive decline. This knowledge will be crucial in developing safe and personalized treatment plans.

This review explores the current understanding and prospects of targeting neurogenesis for the treatment of cognitive impairment. It reviews the relationship between the dysregulation of AHN and cognitive impairment in several common diseases associated with abnormal AHN. While the mechanisms underlying AHN abnormalities require further investigation, this article discusses the mechanisms underlying AHN abnormalities from four perspectives—immunity, metabolism, aging, and pathological changes—based on existing research. Additionally, by comprehensively reviewing both basic research and clinical trials targeting AHN, this review aims to provide valuable insights and a broad perspective for researchers studying AHN and cognitive impairment.

In summary, targeting AHN for the treatment of cognitive impairment has become a significant area of exploration for researchers and clinicians. This review summarizes the mechanisms underlying AHN abnormalities, the relationship between AHN and cognitive impairment, and research on therapies that target AHN. It provides new insights into the potential value of targeting AHN for the treatment of cognitive impairment. This approach not only opens new avenues for addressing cognitive deficits but also offers substantial evidence to support further investment in AHN-related research.

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