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Perspective

Adult hippocampal neurogenesis in Alzheimer's disease: A roadmap to clinical relevance

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SUMMARY

Adult hippocampal neurogenesis (AHN) drops sharply during early stages of Alzheimer's disease (AD), via unknown mechanisms, and correlates with cognitive status in AD patients. Understanding AHN regulation in AD could provide a framework for innovative pharmacological interventions. We here combine molecular, behavioral, and clinical data and critically discuss the multicellular complexity of the AHN niche in relation to AD pathophysiology. We further present a roadmap toward a better understanding of the role of AHN in AD by probing the promises and caveats of the latest technological advancements in the field and addressing the conceptual and methodological challenges ahead.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of age-related dementia, causing progressive memory loss and cognitive impairment. AD is traditionally characterized by two main pathological hallmarks: extracellular plaques, primarily consisting of the β amyloid peptide (Aβ), and intracellular neurofibrillary tangles (NFTs), composed of hyperphosphorylated TAU (pTAU).[1] Previous research has shown that aberrant deposition of Aβ and NFTs leads to synaptic damage, neuronal dysfunction, and ultimately, progressive cognitive decline.[2,3]

The hippocampus, a critical hub for cognition and memory, is one of the first brain regions to be affected in AD patients.[4] The dentate gyrus (DG), a hippocampal subfield implicated in learning and memory, particularly in pattern separation, shows substantial age-related functional decline in humans,[5,6] non-human primates,[7,8] and rodents.[8,9] The DG is further unique as it contains the so-called "neurogenic niche," wherein stem cells continue to generate new neurons in the adult brain, in a special form of cellular plasticity referred to as "adult hippocampal neurogenesis" (AHN).[10] Adult-born dentate granule cells (aDGCs) functionally incorporate into the granule cell layer of the DG as part of the hippocampal circuitry, where they, via their unique physiological properties, play key roles in neural plasticity and cognition.[11–15] AHN has been shown to be impacted by (several aspects of) AD pathology in both rodents and humans.[16,17]

Despite a substantial focus on amyloid and TAU pathologies over the past decades, disease-modifying therapies for AD are still lacking. Hence, "mapping" the full mechanistic heterogeneity of AD, i.e. beyond Aβ and TAU, is an important critical step to developing novel therapeutic targets.[18] Key mechanistic questions as to what renders an individual vulnerable or resilient to developing AD remain unanswered, but may be "hidden" in the brains of a unique group of elderly individuals with preserved cognition, despite the presence of substantial AD pathology.[19,20] This "cognitive reserve" that is apparent in these subjects may likely increase resilience toward developing dementia.[19] Notably, AHN levels in postmortem brains were recently correlated with ante-mortem cognition in mild cognitive impaired (MCI) and AD patients, pointing toward a potential active role of AHN in the buildup of cognitive reserve, which can later on confer resilience to AD-related dementia.[21,22]

As AHN can modulate the DG, the gateway to memory formation, changes in AHN may have physiological implications for the greater hippocampal formation and its cortical inputs and from there, functional effects on learning and memory.[12,23,24] Yet, the exact characteristics of the neurogenic cell populations that exist in the adult and aging human brain, how they impact function and are impacted themselves by AD progression, whether or not they are involved in cognitive reserve, and what the therapeutic relevance of specific pro-neurogenic signals may be, are all questions that remain to be elucidated.

Here, we critically discuss current knowledge on the putative role of AHN in AD pathophysiology and resilience, focusing primarily on the human brain. We emphasize the importance of the multicellular complexity of the neurogenic niche where AHN resides, and hence the relevance of integrating both intrinsic and extrinsic signals from distinct cellular populations,

into any future therapeutic strategies aimed to "rejuvenate" the AD brain. Lastly, we probe the promises and challenges that novel technologies aimed at profiling human AHN entail, and from there, we propose a framework to move the field forward.

PROFILING AHN IN THE HUMAN BRAIN: CURRENT STATE OF THE ART

Determining the presence of hippocampal neurogenesis in the human brain and the putative resemblance to its rodent counterpart has been difficult due to technical and methodological limitations and the study of human brains *per se*. A series of recent studies have employed either distinct histological approaches or single-nucleus transcriptomics to study AHN in postmortem human hippocampal tissue.[25–29] Their opposing results have, yet again, re-ignited a debate on the occurrence and relevance of AHN in humans.[30,31]

The first convincing support for human AHN in postmortem human brain specimens was based on bromodeoxyuridine (BrdU) labeling, traditionally used to label dividing cells and trace their progeny *in vivo*. In an early, highly influential study, neurogenesis was demonstrated in a small series of postmortem hippocampal samples of cancer patients, where BrdU had been administered for diagnostic purposes.[32] Taking an alternative route, Jonas Frisen's group later confirmed the presence of neurons generated during adult life in the DG using carbon-14 (^{14}C)-based retrospective birth dating, providing further support for the existence of human AHN.[33] However, subsequent immunohistochemical studies aiming at identifying neural progenitor cells (NPCs) or immature neurons in the adult human hippocampus have reported highly variable degrees of AHN that might to some extent be explained by methodological variables.[27,30,34–40]

There is also substantial, yet indirect, support for human neurogenesis from studies in which neurogenic subpopulations, such as NPCs, could be isolated from the adult human brain, further revealing its neurogenic potential, and sometimes even correlating it with ante-mortem cognitive measures.[41–44] Currently, each of the experimental strategies used to identify and visualize NPCs and progeny in human brain comes with its own limitations and possible methodological confounders that have to be cautiously considered. Ultimately, monitoring AHN in living subjects would provide the ultimate proof for its occurrence in the adult human brain. Yet, although much progress has been made,[45] non-invasive imaging approaches to visualize potential NPCs in humans have until now lacked the required degree of cell type specificity.[46]

SINGLE-CELL TRANSCRIPTOMICS AS A NOVEL TOOL TO SURVEY HUMAN NEUROGENESIS

Given the cellular complexity of the neurogenic niche in humans, single-cell transcriptomics was put forward as a promising method that could help advance the field.[31,39,47–49] Using single-cell RNA sequencing (scRNAseq) in mouse DG, we and others recently demonstrated that the adult neurogenic niche is a spatially defined complex multicellular system[50–53]; within this small subfield, neural stem cells (NSCs) and their progeny form a tightly regulated continuum of cell states[50–52] supported by other niche-resident cells, like diverse neuronal populations, niche-specific microglia, astrocytes, oligodendrocytes, and specialized vasculature.[50,54–58]

scRNAseq has also been deployed to profile the human hippocampus.[26,28,29,47,59,60] In an earlier study, Habib et al. identified a small population of cells in the adult human hippocampus, annotated as "NSCs" based on the expression of some putative neurogenic markers.[60] However, a recent meta-analysis of this dataset[31] concluded that this cellular cluster could consist of hippocampal ependymal cells that may have been mis-classified in the original study. More recently, Ayhan et al. reported the single-cell transcriptomic profiling of the hippocampal anterior-to-posterior axis using surgically resected samples from five epilepsy patients. Yet, apart from the major neuronal (including DG cells [DGCs] and pyramidal neurons) and glial subtypes, no NSC- or other progenitor-like cells were identified in this relatively small dataset.[59]

Very recently, three comprehensive single-nucleus transcriptomic studies focusing on the adult human DG have yielded conflicting results: two did depict populations with NSC or immature neuronal characteristics,[28,29] while one failed to identify any neurogenic populations.[26] With respect to AD, only Zhou et al. employed a small cohort of AD patients in their single-nucleus transcriptomic profiling of the DG, as discussed below.[29] In addition, there is currently one preprint reporting on the profiling of single-nucleus transcriptomes in the whole hippocampus and entorhinal cortex (thus not focusing on the DG *per se*) of 65 individuals from the ROSMAP cohort at early and late pathology stages, which reported only the main neuronal and glial (sub)populations.[47] Hence, despite the application of these novel technologies, several questions remain largely unanswered: how widespread is human AHN, which cellular populations and biological pathways are critical to sustain or boost it, and how does it mechanistically interact with AD?

EVIDENCE FOR IMPAIRED AHN IN AD PATIENTS

Recent evidence suggests that cellular populations with putative neurogenic or immature features in the adult human hippocampus are affected in AD (for a systematic review of all prior studies, see Terreros-Roncal et al.[61]). Moreno-Jiménez et al. studied the extent of AHN in high-quality and optimally preserved human brains of 58 individuals (13 neurologically healthy control subjects and 45 patients with AD at distinct Braak stages) and observed a marked and progressive decline of the number of DCX$^+$ cells (defined as immature neurons by co-expression of DCX and other immature neuronal markers) as the disease advanced.[30] Although the DCX$^+$ population was further reduced in patients at severe disease stages, a significant decrease in AHN already started in individuals at Braak stages I/II relative to neurologically healthy subjects, which did not match the mild decline in healthy subjects during physiological aging. These findings strongly support AD as a condition that differs from physiological aging and suggest that, in addition to mild AHN reductions owing to normal aging, independent neuropathological mechanisms could contribute or be related to the AHN impairment in AD. Shortly after, putative Nestin$^+$/SOX2$^+$/Ki67$^+$ neural progenitors and DCX$^+$ cells with neuroblast/immature

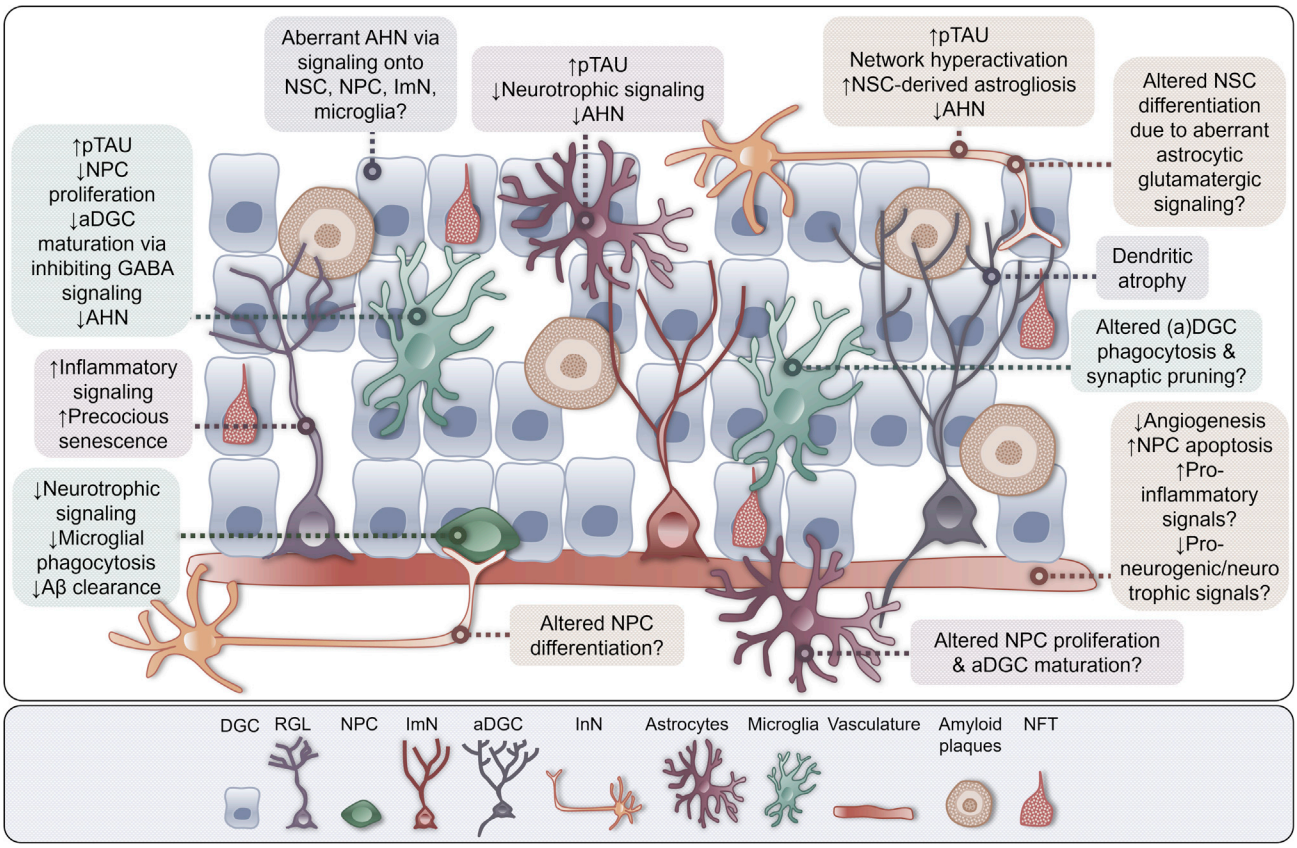

Figure 1. Disruption of homeostasis at the hippocampal neurogenic niche in Alzheimer's disease: Putative cellular and molecular correlates
AD pathology, as reflected in the accumulation of amyloid plaques and neurofibrillary tangles and the loss of neurons in the neurogenic niche of the dentate gyrus, impacts distinct niche-resident cellular populations and intercellular signaling pathways. Captions with question marks indicate observations that have not been directly validated in AD. DGC, dentate gyrus granule cells; RGL, radial glia-like adult neural stem cells; NPC, neural precursor cells; ImN, immature neurons; aDGC, adult-born granule cells; InN, interneurons; NFT, neurofibrillary tangles.

neuronal characteristics were detected in 18 individuals aged 79–99 years during healthy aging and in MCI and AD.[21] Notably the numbers of these populations could be correlated with cognitive performance as a measure of disease progression. The number of DCX^+ cells was lower not only in patients with severe cognitive decline but also in those with MCI. Further, there was a positive correlation between the number of neuroblasts and cognitive diagnosis across patient cohorts.[21] Deficits of AHN in MCI patients may thus precede and possibly promote cognitive deficits in AD.

A recent study employing single-cell transcriptomics in the AD human postmortem DG confirmed a decrease in a neuronal population with immature transcriptional profile compared to samples from healthy control individuals,[29] supporting previous evidence derived from immunohistochemical studies.[21,30] Quantitative analysis within this cellular subpopulation identified 14 downregulated genes in AD associated with synaptic plasticity and signaling. Interestingly, familial and sporadic AD-derived induced pluripotent stem cells (iPSCs) also exhibited early neurogenic changes, and although such systems are far from recapitulating the full complexity of the adult neurogenic niche, these findings again suggest that impairments in AHN could be a potential intrinsic feature of early AD.[62–65]

MULTICELLULAR COMPLEXITY AT THE ADULT HIPPOCAMPAL NEUROGENIC NICHE IN AD

The neurogenic niche in the adult brain is a spatially defined hippocampal subfield wherein NSCs and their progeny are in continuous communication with each other and with other niche-resident, cellular populations and vascular elements and scaffolds (Figure 1). As such, a systematic molecular and cellular profiling of the presumable hippocampal neurogenic niche in human (AD) brain will be key to assessing the role of AHN in AD progression and resilience, and it will help identify distinct cell types and cell states involved in AD etiology that may be differentially amenable to possible therapeutic interventions.

Neuronal subtypes

Granule cells are the most abundant neuronal population in the DG. In the rodent brain, DGCs have been shown to receive excitatory inputs from distinct cortical, subcortical, and hippocampal subfields, and subsequently relay pertinent signals onto NSCs and immature aDGCs via secretion of soluble factors.[66–71] Rather surprisingly, not much is known about the impact of AD pathology on mature DGCs in the human brain. While amyloid plaques have been observed, they appear minor in the DG,

which is a subfield that does not undergo major cell loss nor prominent atrophy in AD.[72–74] A significant decrease in the dendritic length of DGCs and differential effects between distal and apical branching at late stages of AD progression have been observed in a small cohort of patients,[75] but whether and how these alterations may impact NSCs and their progeny at the onset of disease progression requires further research.

In rodents, DGCs recruit circuit signals transduced by a wide range of inhibitory interneurons and mossy cells and likely thereby modulate NSC homeostasis, progenitor proliferation and survival, and maturation of aDGCs in a stage-specific manner.[13,67,76–79] Adult NSCs also receive direct inputs from parvalbumin interneurons, which helps them remain quiescent.[80] Reversely, GABAergic signaling onto hippocampal NPCs induces neuronal differentiation.[81] Hence, local network activity appears to be an important determinant of NSC activation. This notion becomes particularly critical from an AHN perspective, considering that the DG circuitry can be not only positively regulated (e.g. by physical exercise[82–84]) but also negatively impacted along physiological aging and in AD.[24,85]

Interestingly, enrichment of pTAU inclusions is observed in interneurons residing in the subgranule zone (SGZ) and hilus of the DG in AD patients and AD mouse models.[86] Of note, overexpression of human TAU in GABAergic interneurons in the mouse brain induced local neural network hyperactivation, increased NSC-derived astrogliosis, and impaired neurogenesis.[86] Thus, widespread hippocampal network dysfunction is a prominent feature of AD pathology, which also impacts the neurogenic niche.[87] Yet, the functional implications of these neuron-specific AD alterations for the neurogenic process along AD progression in the human brain remain largely unknown.

Microglia

Microglia are the brain-resident macrophages, contributing to neuronal homeostasis by continuously surveilling and phagocytosing apoptotic cells and debris and by signaling onto different cellular populations.[88] In the rodent adult hippocampal neurogenic niche, microglia are in close contact with NPCs and DGCs, where they are responsible for the phagocytosis and elimination of both newborn and mature neurons, as well as for the pruning of selected synapses.[89–91]

Recent evidence suggests that niche-resident microglia display unique morphological and transcriptomic signatures specific to the neurogenic niche by upregulating activation-like transcriptional programs and downregulating homeostatic gene expression.[50,54–56,92] Phagocytosis of apoptotic cells promotes a coordinated transcriptional program in DG-resident microglia, which alters their secretome, inhibiting neurogenesis both *in vivo* and *in vitro.*[93] While selective microglial ablation in the DG reduced survival of adult-born neuroblasts,[55] differential context- and activation state-specific effects of microglia on AHN have been reported as well,[67,94,95] consistent with our current understanding of the complexity and diversity of microglial responses and properties.[88,96]

In an earlier study, AHN in mice was induced upon controlled activation by microglial cytokines, mimicking adaptive immunity.[97] Similarly, interleukin-4 (IL-4)-activated microglia increase NPC proliferation and neuronal differentiation in mouse DG,[98] while voluntary running induces insulin-like growth factor-1 (IGF-1) and brain-derived neurotrophic factor (BDNF) expression in DG microglia of aged mice, presumably shifting them from an inflammatory toward a more neuroprotective state.[99,100] Of note, microglia from hippocampi of animals that were exposed to exercise (i.e. running) were able to activate latent NPCs when added to neurosphere preparations from sedentary mice, suggesting that the running-induced increase of AHN is, at least partly, mediated by microglia.[94] Reversely, inflammation-associated microglial activation impairs NPC proliferation, neuronal maturation, and cognition.[97,101–104] Similarly, alterations in the microglial secretome in the aged mouse hippocampus are correlated with the natural decline in NPC activity, mediated primarily via CX(3)CL1 (fractalkine), a chemokine associated with a more neuroprotective microglial phenotype.[94]

Similarly to the healthy brain, accumulating evidence suggests divergent and multilayered functions of microglia in AD pathology.[88] Microglia residing in the DG of human AD brain were shown to develop an aberrant morphological profile that was linked to the accumulation of toxic soluble pTAU species, although the functional implications for the neurogenic capacity within the hippocampal niche of the AD brain remain to be explored.[105] In co-culture with mouse NPCs, microglia carrying familial mutations of presenilin 1 (PS1) could block the inductive effect of IL-4 on NPC proliferation.[106] Interestingly, inhibition of microglial activation or microglial depletion in mouse models of familial AD restored AHN and improved memory and anxiety behavior.[107,108]

Taken together, it will be important for future therapeutic approaches to better understand the functional implications of the differential activation of distinct microglial populations in AD. Also, a systematic characterization of the different microglial subtypes and cell states in the human neurogenic niche—along the AD trajectory—will be particularly instructive.

Astrocytes

In the adult mouse DG, astrocytes are derived from a proliferating local astrocytic population generated by adult NSCs.[58,109] Niche-resident astrocytes are implicated in the proper survival, maturation, and functional integration of aDGCs.[67,110] These effects are mediated by both juxtacrine and paracrine signaling pathways. *In vitro*, astrocytes inhibit neuronal differentiation of cultured neurospheres via Notch signaling.[111] *In vivo*, newly formed synapses of aDGCs are ensheathed by astrocytic processes. Astrocyte-specific blockade of vesicular release reduced glutamatergic synaptic input and spine density in newborn but not mature DGCs,[110] while inhibition of astrocytic glutamate re-uptake also decreased postsynaptic currents in aDGCs,[112] highlighting a close interaction between astrocytes and aDGC function. Recently, single-nucleus transcriptomics in adult human hippocampus revealed distinct molecular signatures between astrocytes isolated from the entorhinal cortex and those residing in DG, with the latter overall expressing remarkably lower levels of GFAP.[113] A gradual increase in GFAP levels with advancing age was, however, observed for both cortical and hippocampal astrocytes.[113] Similarly, a general decrease in the number of S100β-expressing astrocytes with aging was recently observed in the mouse DG[114]; however, the possible functional implications for adult AHN remain unknown.

Similarly to microglia, astrocytes can provide neurotrophic support via secreting BDNF and increasing dendritic outgrowth and spine density in cultured neurons.[115] Interestingly, astroglia-specific secretion of BDNF in the 5×FAD mouse model of AD increased hippocampal synaptic density, increased long-term potentiation (LTP), and improved cognitive performance.[115] Whether and how astrocytic BDNF signals onto aDGCs in the AD hippocampal niche has not been studied; however, BDNF overexpression in hippocampal astrocytes can induce AHN.[116] The pro-neurogenic properties of astrocytes seem to be specific to DG-residing astrocytic populations, since co-culture of adult NSCs with spinal-cord-derived astrocytes did not induce neuronal differentiation.[117] Interestingly, astrocytic proliferation in the adult mouse DG increases upon physical exercise, similarly to what is observed in adult hippocampal NPCs,[109] putatively suggesting an interaction between the enhanced astrocytic pool and the neurogenic trajectory.

In the human AD brain, an aberrant accumulation of TAU was recently observed in astrocytes residing in the hilus of the DG.[118] Tau overexpression in hilar astrocytes in mice reduced the numbers of both newborn neurons and interneurons and in parallel induced spatial memory impairment.[118] Although these observations were associated with abnormal astrocytic mitochondrial transport and function, other mechanisms, like altered gliotransmitter or cytokine release, cannot be ruled out. Indeed, astrocyte-specific release of interleukin-6 (IL-6) in adult mouse DG impaired NPC proliferation, survival, and neuronal differentiation.[119] Further insights from single-cell profiling studies, specifically in human (AD) DG, could shed light on niche-specific mechanistic correlates between astrocytes, other glial populations, and the neurogenic process *per se*.

Vasculature

The DG is a highly vascularized brain region, where blood vessels provide trophic and neurogenic factors, nutrients, and structural support to both aDGCs and mature DGCs.[120,121] Also, NPCs and NSCs are in close proximity to blood vessels,[57,122] as a number of capillaries cross the granule cell layer toward the hilar side and then change direction and align with the SGZ in a rostral-to-caudal direction.[122] Blood flow velocity is correlated with exercise-induced AHN,[123] while neurovascular coupling is required for the induction of AHN in a novel environment.[124] Vascular endothelial growth factor (VEGF)-induced DG neovascularization was further shown to be associated with a significant increase in AHN.[125–127] In addition, vasculature-derived IGF-1 can promote neurogenesis.[124,128,129]

In vitro, human hippocampal NPCs treated with human serum from older donors showed increased apoptosis compared to those incubated with serum from young individuals, further supporting the importance of the systemic milieu for the survival of NPCs in the aged brain.[130] Of note, in a similar assay, increased apoptosis in human hippocampal NPCs was associated with an increased propensity of the serum donors for developing dementia.[131] Along the same lines, heterochronic parabiosis experiments in mice demonstrated that an old "systemic environment" decreases AHN and impairs memory in younger animals, possibly due to the secretion of pro-inflammatory cytokines like CCL11[132,133]. In mice, an age-dependent decline in vascularization and increases in blood-brain barrier leakiness have been reported.[114] In addition, vasculature impairment in the hippocampus, and in particular in the molecular layer of the DG, was reported in AD mouse models.[134] Vasculature alterations in the DG of aged individuals or AD patients have not been studied extensively. However, recent evidence showed decreased angiogenesis, neuroplasticity, and progenitor numbers in the anterior DG of older individuals compared to younger tissue.[34]

Intercellular crosstalk

Adult NSCs and their progeny need to precisely integrate a plethora of signals from the niche, including those from DGCs, microglia, astrocytes, endothelia, and long-range neuronal projections to the DG, notably in an activity- and age-dependent manner.[67,87,135–137] Despite its name, NSC quiescence was actually suggested to reflect a rather "active" state maintained by distinct signaling interactions within the niche.[138] Of interest, several secreted factors (e.g. Notch, Wnt, SHH, FGF, and BMP) that have been reported as AHN regulators are deregulated in AD, yet the direct impact of these aberrations on the neurogenic process remains largely elusive (for systematic reviews, see Vicidomini et al. and Hollands et al.[67,139]).

Rather surprisingly, adult NSCs harbor intrinsic inflammatory properties under homeostatic conditions, which need to be proactively suppressed in order to enable their proliferative and differentiation capacity.[140,141] Conditioned medium from cultured NPCs could induce microglial functions, such as phagocytosis, chemotaxis, and proliferation, primarily via VEGF.[142] Interestingly, a pathology-dependent loss of immunomodulatory and neurotrophic properties of NPCs derived from the subventricular zone (SVZ) of AD mice has been previously observed.[143] Thus, while the putative physiological relevance of this gene ontology remains unclear, these findings underscore the significance of the local intercellular crosstalk between AHN and immunomodulatory signaling in both physiological and pathological conditions.

As part of another intricate intercellular communication network, DG interneurons secrete the endogenous neuropeptide cholecystokinin (CCK), which via an astrocyte-mediated glutamatergic signaling cascade induces neuronal differentiation of adult NSCs.[144] Similarly, neuron-derived fractalkine promotes AHN via binding its receptor, CX3CR1, in microglia.[94,145] In conditions of chronic stress, IL-4-activated microglia promote AHN via BDNF signaling in mice.[98] Such interactions may become particularly important under inflammation-prone conditions, like aging and neurodegeneration. Indeed, during aging, decreased AHN has been linked to increased corticosteroids, BMP signaling, and neuroinflammation, also in the human brain.[28,146,147] Interestingly, an increase in microglia-blood vessel contacts along aging has been recently reported in mouse DG[114]; however, the functional significance of this observation warrants further research. Apolipoprotein E4 (APOE4), the strongest genetic risk factor for developing late-onset AD, was shown in earlier studies to impair aDGC maturation via GABA signaling inhibition.[148] Recent *in vitro* evidence suggested that APOE4 impairs microglial lipid homeostasis, triggering pro-inflammatory signals that disrupt neuronal activity.[149] Moreover, adult NPCs derived from the AD mouse SVZ were shown to exhibit decreased trophic properties and a diminished potential for supporting microglial phagocytic activity and Aβ clearance,[143,150]

further highlighting the putative functional significance of the niche microenvironment in AD. Yet, the precise mechanistic underpinnings of such intercellular interactions in the human AD niche remain to be elucidated.

Cellular senescence and quiescence at the neurogenic niche

A dramatic reduction in hippocampal neurogenesis takes place in early adulthood, followed by a slower, more gradual decline during aging in both mice[151] and humans.[30,33,34] Cellular senescence is a dynamic, multifaceted process that results in cell-cycle arrest upon a variety of stressors or physiological signals.[152] Cellular senescence can be attributed to both intrinsic characteristics of NSCs and the niche microenvironment and has been directly linked to not only physiological but also pathological aging, including AD.[153,154] Senescence-like molecular signatures were recently profiled in neuronal populations in human AD brain and in AD-patient-derived directly induced neurons in culture, involving—among others—metabolic alterations and pro-inflammatory signals.[155] Whether such signatures are also present in postmitotic DGC (sub)populations in AD and, if so, how they may impact niche-resident neurogenic populations is not known. Age-dependent transcriptional, genetic, epigenetic, metabolic, hormonal, inflammatory, and proteostatic alterations in adult NSCs and other niche-resident cellular populations have all been implicated in reduced NSC functionality in the aged brain.[114,136,156–161] Increased inflammatory signals and non-canonical Wnt signaling, in particular, were shown to shift adult NSCs in the aged SVZ toward quiescence, limiting their activation and proliferation potential, although senescence signatures were not monitored in the same context.[141] An age-dependent increase in the expression of specific senescence markers was also observed in the NSCs of the SVZ.[162] However, NSC and progenitor senescence in the aged (human) DG has not been systematically studied to date.

Declined progenitor numbers and function were found to be correlated with $p16^{Ink4a}$, which is a cyclin-dependent kinase inhibitor negatively regulating the cell cycle and linked to senescence in the SVZ, but not in the DG.[163] However, in another study, senescent NPCs were found in the DG of mice, and their ablation increased NPC proliferation and neurogenesis.[164] Increased genetic and epigenetic instability and neuroinflammation were also observed in the non-human primate DG upon aging.[165] A shift toward quiescence was recently shown to impair homeostasis and function of adult NSCs in the aged mouse hippocampus, promoting distinct molecular signatures related to epigenetic and transcriptional dysregulation, inflammation, metabolic and proteostatic alterations, cellular stress, and DNA repair[166]; however, whether these dynamic changes involve senescence-related pathways remains unknown.

Mitochondrial dysfunction in adult hippocampal NSCs has also been associated with reduced neurogenesis in the aged brain.[167] Interestingly, NSCs isolated from human AD postmortem tissue showed decreased viability and precocious senescence compared to NSCs from controls.[43] Even though the implications of these findings in pathological conditions have not been studied yet, it has been proposed that elimination of certain subpopulations of senescent and/or quiescent progenitors could potentially be employed to reverse the slow AHN rate in AD.[136] Overall, cellular quiescence and senescence are two relatively understudied phenotypes with some major putative functional implications for physiological aging and AD. Evidently, further research into quiescence- and senescence-related cellular and molecular profiles in the AD DG is required to identify mechanistic checkpoints that could be potentially targeted in therapeutic strategies.

AHN AND AD: A POTENTIAL LINK TO RESILIENCE?

Human studies

Somewhat counterintuitively, histopathological changes associated with AD, Aβ, and TAU pathologies have also been documented in postmortem brains of non-demented, older individuals. Several terms have been used to describe these non-demented subjects, including—but not limited to—resilient to AD, non-demented with AD neuropathology (NDAN), and "cognitive reserve" individuals (for review, see Kok et al.[168]). The existence of resilient individuals, who remain cognitively intact despite the presence of substantial Aβ and TAU pathology, suggests that the human brain can naturally resist or significantly delay the effects of these neurotoxic events that may otherwise lead to cognitive impairment in AD. However, the mechanistic underpinnings of this increased tolerance to AD pathology and what underlies an enhanced cognitive resilience remain largely unknown.

Briley et al. found that the number of $SOX2^+$ cells with putative NSC-like characteristics was significantly increased in the DG of NDAN individuals as compared to AD subjects.[169] The prevalence of this cellular subpopulation positively correlated with preserved cognitive function, and these authors concluded that sustained AHN in the DG of NDAN subjects is an important factor in preserving their intact cognition, notably despite the presence of plaques and NFTs. In support, we also demonstrated that the prevalence of DCX^+ cells positively correlates with better cognitive scores in both AD and MCI patients[21] and further showed that the levels of a DCX^+ and $PCNA^+$ cellular subpopulation (possibly reflecting neuroblasts) were associated with the functional interaction of the presynaptic SNAP Receptor (SNARE) proteins, syntaxin and SNAP-25[21].

Thus, the level of AHN is associated with both higher cognitive score and increased levels of critical synaptic proteins and is associated with intact cognition, irrespective of the presence of AD pathology in a subgroup of patients. Of note, AD, and also MCI, patients are furthermore often impaired in AHN-related tasks, like spatial orientation and pattern separation.[170,171] These observations together suggest that targeting AHN could be a valuable putative therapeutic approach to counteract cognitive impairment and promote synaptic resilience in AD, and that reduced AHN in AD may—partially—account for cognitive dysfunction in the disease.

Animal studies: Contribution of AHN impairment to cognitive decline in AD

Studies using AD transgenic mouse models have generated mounting evidence implicating alterations of AHN in AD pathology. These mouse lines include (combinations of) familial AD (FAD)-associated mutations in *amyloid precursor protein* (*APP*) and/or *PS1*, as well as in the gene encoding the microtubule-associated protein TAU (*MAPT*). The majority of these

studies reported decreased AHN in early stages of AD.[172–174] More specifically, the APP^{swe}PS1$^{\Delta E9}$ mouse model showed severe reduction in NPC proliferation, as well as neuronal differentiation at 2 months of age, when Aβ plaques were not yet evident,[153] and notably before the occurrence of cognitive deficits.[175] 5×FAD mice also exhibited impaired AHN starting at 2–3 months of age[176] prior to amyloid deposition[177] or cognitive dysfunction.[176] Reduced AHN was detected in 3×Tg mice already starting at 2 months, before the accumulation of Aβ plaques and pTau/NFTs[178] with memory impairments not apparent before 4–5 months in this line.[179]

The observation that AHN impairment occurs prior to the accumulation of AD hallmarks and the appearance of cognitive dysfunction suggests that AHN impairment may have a causative role in the cognitive decline along AD disease progression. Along these lines, ablation of AHN indeed exacerbated cognitive dysfunction in APP^{swe}PS1$^{\Delta E9}$ mice[180] and in 5×FAD mice.[176] In two other studies from the same group, ablation of neurogenic populations was reported to improve synaptic plasticity and cognitive function in APP/PS1 and hAPP-J20 mice.[181,182] In the first, Gfap-expressing cells were depleted, while in the second one, all proliferating cells were eliminated. Both approaches targeted a wide range of populations that included all astrocytes in the former and all proliferating cells in the brains of familial AD mice in the latter, which may have comprised—among others—microglia and astrocytes. Elimination of disease-associated microglial and astrocytic subpopulations in AD may underlie the apparently beneficial effect.[108,183]

While AHN-specific tests for changes in pattern separation, as those also found in AD patients,[171] still need to be performed in most AD models, this already demonstrates that AHN impairment *per se* induces cognitive deficits in rodent models of AD. Therefore, enhancing functional AHN, preferentially in the earlier stages of AD, may help increase brain reserve, which could be a potential therapeutic strategy for AD treatment.

Animal studies: Strategies to modify AHN in AD models—impact on cognition

A series of studies aiming at increasing AHN in rodent models of AD have further provided experimental proof-of-concept for the notion that AHN stimulation may benefit cognitive functions in AD. Recently, we identified miR-132, a microRNA strongly downregulated in AD, as a potent positive regulator of AHN in mice and in cultured human NSCs.[53] Overexpression of miR-132, by intracerebroventricular injection of a synthetic miR-132 mimic oligonucleotide, ameliorated AHN deficits in APP/PS1 and APP knockin (*App*$^{NL-G-F}$) mice, and in parallel successfully restored memory deficits in *App*$^{NL-G-F}$ mice in passive avoidance and pattern separation tests. Subsequently, blocking the proliferation of progenitor cells in miR-132-overexpressing AD mice abolished memory rescue in the passive avoidance test, confirming that AHN is a prime component of miR-132 regulation of contextual memory performance in this task. Interestingly, the miR-132-related processes included NPC proliferation, neuronal differentiation, survival, functional integration, and neurotrophic signaling (like e.g. BDNF), suggesting that a synergistic contribution of cell-intrinsic and cell-extrinsic signals is necessary for a potent pro-neurogenic effect.[53]

Along the same lines, increasing AHN alone, either genetically (by a viral infection to express WNT3 protein) or pharmacologically (by P7C3, a compound that improves the survival of new neurons) had minimal effects in ameliorating cognitive dysfunction in 5×FAD mice.[176] However, increasing AHN by exercise did improve cognitive abilities in 5×FAD mice. In addition to an increase in AHN, exercise led to an increase in the levels of hippocampal BDNF. Genetic and pharmacological treatments that simultaneously induced AHN combined with a treatment to increase levels of BDNF ameliorated cognitive dysfunction in 5×FAD mice despite the presence of stable levels of amyloid plaques. Although BDNF infusion into the hippocampus could improve cognitive performance in a rat model of AD induced by $A\beta_{42}$,[184] increasing BDNF alone, without promoting AHN, was not sufficient to improve cognitive function in 5×FAD mice.[176] Together, these findings highlight the significance of considering the "fitness" of the entire niche microenvironment as a *sine qua non* for AHN targeting.

Enhancing maturation and functional integration of aDGCs into the existing granule cell network, without increasing their number, has also been shown to improve cognitive function in AD. Richetin et al. identified Neurod1 as a potent candidate to direct adult hippocampal progenitors toward an exclusive neuronal fate and to stimulate their terminal neuronal differentiation.[185] Selective Neurod1 gene delivery to adult neural progenitors increased dendritic spine density only of the newborn neurons in APP^{swe}PS1$^{\Delta E9}$ mice to the same level as that observed in wild-type mice. The increased connectivity of only the adult-born neurons in this mouse model led to a restoration of spatial memory, further highlighting the important role of AHN for cognition in AD.

NOVEL APPROACHES, REMAINING CHALLENGES, AND OPEN QUESTIONS

A series of conceptual and methodological roadblocks, discussed below, could explain —at least partially— the conflicting findings and the current scarcity of a mechanistic understanding of the exact role of AHN in human AD[39,49] (Figure 2). Overcoming these will yield more consistent results and will also enable a better application of current findings to future therapeutic development.

Human brain tissue quality

As discussed before, studies on human AHN in AD have, to date, been primarily performed in postmortem, fixative-preserved brain tissue. Such approaches come with considerable limitations, mostly due to variable postmortem delay (PMD) and suboptimal tissue fixation, both of which can critically impact the quality of immunolabeling against specific neurogenic markers: target antigens decay at different rates following death or differentially react to distinct fixation conditions or agonal states.[37,39,61,186,187]

Similarly, tissue quality and RNA stability, as reflected in the RNA integrity number (RIN), are also pivotal for successful scRNAseq applications.[188–191] Having access to high quality, short-PMD and high-RIN archived brain tissue samples is challenging but pivotal[27,39,192]: tissue collection and processing practices at biobanks worldwide differ and often do not align

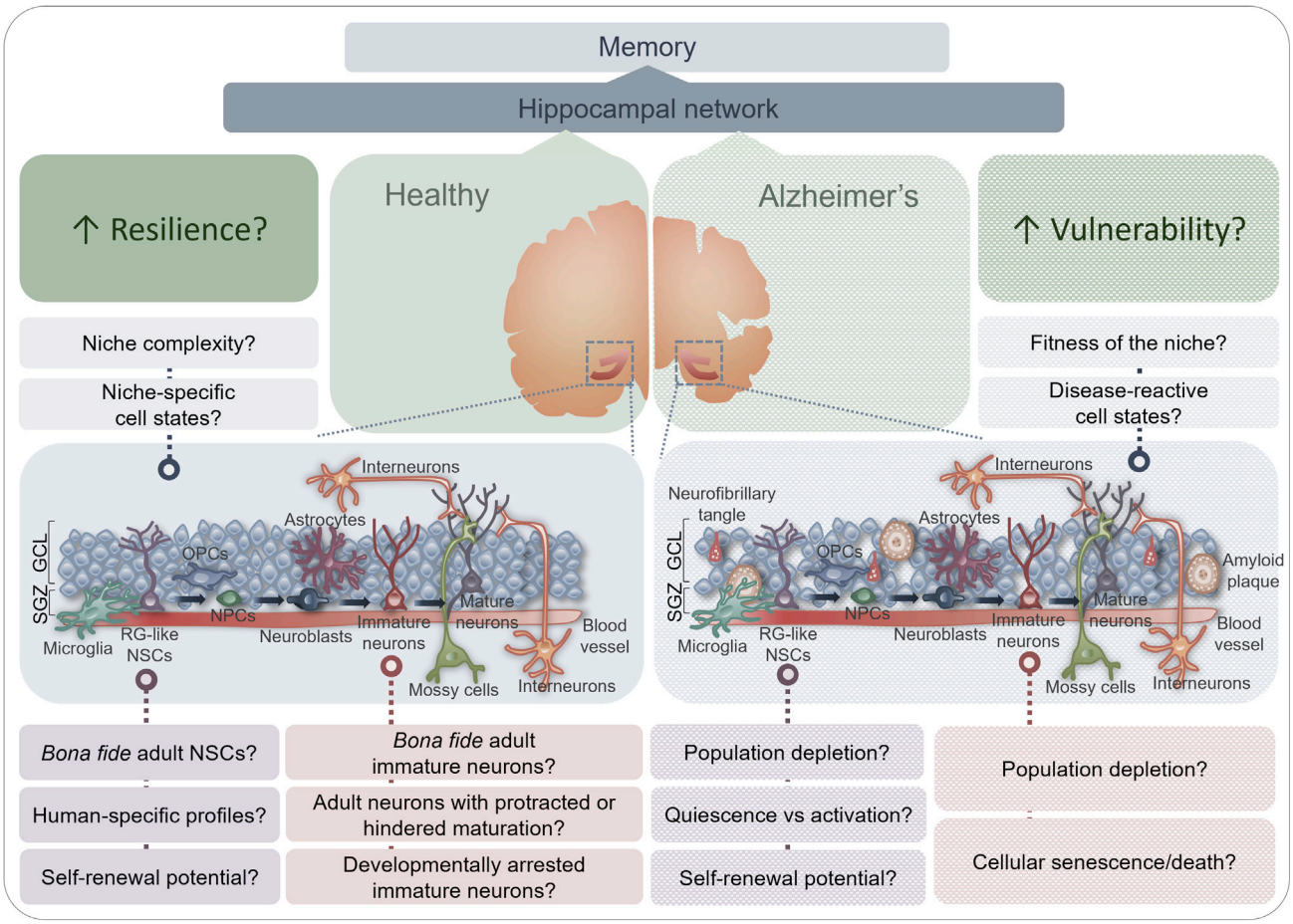

Figure 2. Adult hippocampal neurogenesis in Alzheimer's disease: Open questions
Remaining issues to address in order to "map" the potential role of AHN in healthy (human) brain and in AD pathology, and to identify AHN-specific signatures of resilience or vulnerability to disease, are displayed. Missing mechanistic insights will help assess the therapeutic relevance and the potential of recruiting AHN to "rejuvenate" the hippocampal network and boost memory in AD. SGZ, subgranular zone; GCL, granular cell layer; RG-like NSCs, radial glia-like neural stem cells.

with the requirements for optimal AHN detection, which becomes critical when comparing matched groups of disease versus control cases.

Sample stratification

Another major issue complicating data interpretation is the observation that next to environmental factors like exercise, stress, or medication, neurogenesis rates have been associated with a series of pathological conditions (e.g. status epilepticus, depression, AD). Hence, a thorough clinical documentation for each donor is a prerequisite not only for accurate patient stratification, but also for the inclusion of properly matched control samples. Confounding factors that can compromise the results and impact their interpretation include, among others, co-existing pathologies and comorbidities, medication, agonal state, and ante-mortem cognitive performance.[39]

Evidently, identifying donors who fulfill specific selection criteria becomes particularly challenging in aged cohorts, as is the case for sporadic, late-onset AD. Even though scRNAseq approaches could in principle hold great promise for the assessment of the neurogenic potential of the adult human brain, some of the recent single-nucleus RNA sequencing (snRNAseq) studies in adult human hippocampus either did not provide adequate clinicopathological information on their donors or used brain specimens with possibly interfering pathologies (e.g. epilepsy).[28,59,60]

Marker specificity in human brain

As all our current knowledge on "neurogenic" markers has been inferred from rodent studies, the choice of markers for the study of human AHN is another key variable contributing to inconsistencies across the literature.[26,31,39,193,194] Earlier histological studies and more recent single-nucleus transcriptomics in human hippocampus have questioned the specificity, and hence the uniform use across species, of such markers for human adult NSCs and their progeny.[26,28,29,31,48,194] Apart from a putative issue in histological studies, the current paucity of reliable human neurogenic markers can also impact the validity of single-cell transcriptomic approaches that base cell type annotation on pre-defined sets of mouse-inferred markers.[26,50]

Indeed, snRNAseq datasets from the human adult hippocampus suggest that the transcriptional profiles derived from human

and mouse DG do not fully overlap.[28,29,59,194] Yet, one of the recent snRNAseq studies that actively attempted to identify NSCs and progenitors in the adult human DG, but yielded negative results, still assumed a high degree of cross-species conservation[26]: the authors searched for overlap between mouse and human datasets and employed mouse-specific markers with questionable specificity in human brain.[31] However, in two of these very recent snRNAseq studies, both NSCs[28] and immature neurons[28,29] were successfully identified in the human adult neurogenic niche.

Different factors might account for these discrepancies. Wang et al.[28] proposed that a low inflammatory index is critical for the preservation of neurogenic populations and that increased inflammation levels may have impeded their identification in the Franjic et al.[26] dataset. In addition, Zhou et al.[29] had to implement machine learning analytical approaches in order to reliably delineate an immature neuronal cluster in their dataset, again suggesting that conventional marker-based strategies may not be sufficient for the profiling of rare (as discussed below) and previously uncharacterized populations in the adult human neurogenic niche. Interestingly, although small progenitor-like cell clusters (LPAR1$^+$ and PAX6$^+$ cells[47,59]) have been identified in some of these datasets, these findings were not further investigated.

Scarcity of NSCs and progenitors

Of note, based on current histological data, putative *bona fide* adult NSCs and their progeny may be particularly rare in the aged human neurogenic niche and might further decline in AD. Reliable identification of such scarce populations, using for instance snRNAseq, also requires the profiling of adequate cell numbers, notably at a sufficiently high sequencing depth. In addition, reconstructing differentiation trajectories (which would be particularly necessary to identify lineage relationships between NSCs and progeny in adult brain[26,52,194]) from single-cell transcriptomic data heavily relies on sufficient sampling of cells that transition between different states in the lineage trajectory.[195] Along these lines, analyzing anatomical substructures of the DG targeted by microdissection may be necessary to enrich for cellular populations of interest and thereby ensure that any significant alterations between groups of individuals can be detected.[47]

Not all recent studies deploying snRNAseq to profile the adult human hippocampus were adequately powered, in terms of either granule cell numbers or sequencing depth. This may interfere with the resolution or the accuracy of the subsequent cell type clustering and annotation. In addition, cellular populations of putative interest for AHN were in certain cases removed from the analysis due to their small size,[26,59] suggesting that some valuable information might have been missed.

Methodological and computational challenges

Mapping the full complexity of the AHN niche in AD, and identifying the cell types and cell states that may be most amenable to therapeutic intervention, is challenging and cannot be solely achieved by tissue-level resolution (bulk) approaches or immunohistochemical studies.[47,196–198] Single-cell resolution, genome-wide, molecular profiling can offer valuable complementary insights, as recently demonstrated in rodent or primate DG.[26,28,29,50–52,194] Among others, analysis of these datasets further enables *in silico* reconstruction of lineage trajectories, or "trees," by projecting cells onto a "pseudotime" axis, according to their activation/differentiation transcriptomic profile, or by predicting the direction of differentiation of a given cellular population.[199,200]

Yet, such retrospective differentiation trajectories do not necessarily reflect clonal relationships between cells, as genetic lineage tracing methods would do.[195] In addition, these approaches cannot differentiate between adult-born, immature neurons and developmentally generated granule cells with retained immature profiles due to—among other reasons—protracted differentiation.[29] Hence, when profiling the human AHN niche in postmortem brain, novel computational tools that can address these issues would be of particular relevance to identify rare stem cell and progenitor populations in a more unbiased and reliable way.[195,201–203] Notably, fate mapping of newborn neurons in adult human brain sections was recently implemented, demonstrating the intrinsic regenerative potential of these cells *ex vivo*.[29] Such approaches are instrumental, as they provide proof-of-concept for the ability of the adult brain to generate new neurons and will therefore be particularly informative in delineating mechanisms that could be used to leverage neurogenesis in AD.

In addition, integration of single-cell transcriptomics, epigenomics, and spatial transcriptomics from the same tissue was recently shown to increase robustness and validity of cell type classification and cell state identification in complex populations, such as the hippocampal neurogenic niche.[204–206] Such cross-modal analysis was recently also implemented to reconstruct a multimodal cell census and atlas of the mammalian primary motor cortex within the BRAIN Initiative Cell Census Network.[204] Similarly, multi-omics integration recently allowed the identification of cell-type- and state-specific, disease-associated *cis*-regulatory elements, their candidate genes, and their association with genetic risk in human AD cortex.[205]

FUTURE PERSPECTIVES: IS AHN A REALISTIC THERAPEUTIC TARGET IN AD?

Taken together, the evidence discussed here suggests that AHN may play a critical role in the progression of, or the resilience to, AD pathology. Restoring and/or stimulating endogenous AHN, along with enhancing the "fitness" of the DG niche in subjects at high risk for AD, could emerge as an effective strategy to prevent the onset and/or counteract the progression of the disease by promoting the regenerative and recovery process. Given the interaction between AHN and AD pathology (e.g. amyloid and pTAU), such strategies could also be used as adjunct therapeutics to existing treatments to maintain cognition or prevent its decline by providing synergistic effects on hippocampal function and plasticity.

Yet, could the (re)activation of "resting" NSCs and a mere and timely addition of new neurons to the AD hippocampus be sufficient to halt or prevent memory decline? Recently, we reported that augmenting hippocampal neurogenesis in 5xAD mice rescues hippocampus-dependent memory, not only by increasing the recruitment of immature neurons into the memory circuit, but also by restoring spine density deficits in mature granule

neurons in the DG,[15] suggesting that newborn neurons can exert non-cell-autonomous effects on the DG neuronal network. Yet, aDGCs are low in number as compared to the degenerating neurons in AD, and AD pathology extends beyond the hippocampus. Therefore, it is unlikely that stimulating AHN will achieve global repair in advanced stages of AD. However, the selective presence of AHN in the DG represents a highly strategic location in the trisynaptic circuit of memory processing and formation, and "rejuvenating" the origin of that circuit, provided intervention starts on time, could help preserve and possibly even promote its function and from there, the hippocampus as a whole, and the subsequent cortical regions that receive its input.

Although the causal links between AHN decline and AD in humans still need to be addressed,[136] it will be important to understand how AHN impacts functional connectivity and hippocampus-dependent behaviors. Previous reports suggest that the DG withstands the formation of amyloid plaques, NFTs, and neuronal death until late stages of AD. However, more subtle intrinsic morphological, transcriptional, or epigenetic alterations may contribute to memory alterations observed already at early stages of AD.[207] Indeed, a recently postulated, interesting hypothesis has proposed a link between AHN and early AD degeneration of the lateral entorhinal cortex, which provides the main afferent connections to newly born neurons in DG: early exposure of axonal terminals to a putatively toxic cellular and molecular environment in the AD niche may result in retrograde damage of neuronal bodies in the lateral entorhinal cortex.[208] Since causal relationships cannot be definitively established from cross-sectional data in postmortem studies, experimental validation is required to probe putative, cell-type-specific molecular mechanisms that became available from genome-wide screening studies, allowing a better understanding of the links between AHN and AD pathophysiology.

Human-relevant systems (e.g. mice carrying human AD mutations or engrafted with human progenitors, or patient-derived *ex vivo* [two- or three-dimensional] cell cultures) can address not only causality regarding novel hub regulators of AHN in AD, but also the contribution of common genetic risk factors. Notably, adult-born neurons in rodents have been shown to be pivotal not only for encoding novel experiences, but also for forgetting previously learned ones.[209] Future studies will therefore need to dissociate these two functional aspects in order to leverage AHN to beneficially impact memory in AD. NPCs isolated from human AD brain retain the potential to proliferate and differentiate *in vitro.*[43] Hence, even if AHN levels are attenuated in AD, identifying tractable cell populations, cellular states, and early molecular mechanisms that could be selectively targeted to (re)stimulate the neurogenic process could hold great promise in developing novel therapeutic strategies for AD.

Adult NSCs are commonly perceived as a poor target for regenerative interventions because they are limited in number and are stated to have limited self-renewal capability, suggesting that NSC proliferation that is prematurely or inappropriately induced will presumably result in a depletion of the stem cell pool.[210] Nevertheless, there is evidence for heterogeneous populations of molecularly distinct NSCs and progenitors, some of which may remain more plastic than others.[13,58,166,211] Hence, identifying tractable and putatively druggable targets involved in the intrinsic regulation of quiescence, reactivation, or inflammatory response of NSC or progenitor subsets, during AD progression or in AD resilience, could provide a framework to design novel pharmacological interventions tailored for AD.[136]

As discussed above, the AHN niche is a complex, multicellular system receiving regulatory input from a multitude of intracellular, juxtacrine, and paracrine signals that are disrupted in AD.[58] Of note, our previous work suggests that, along with enhancing AHN, increasing the "fitness" of the niche *per se* (by e.g. boosting neurotrophic signaling) and doing so from early on is required to reverse memory deficits in AD mice.[176] Strikingly, aberrant de-differentiation and "hypo-mature" cellular states have also been reported *in vitro* and *in vivo* as a possible sign of neuronal vulnerability and risk for neurodegeneration in AD.[65,212–214] This further highlights the relevance of an intricate cytoarchitecture that may impact the functional significance of immature neuronal states in such a niche for the DG network and the hippocampus in general. Taken together, these findings emphasize the importance of profiling, understanding, and considering the molecular and cellular complexity of the niche microenvironment when approaching AHN targeting as a therapeutic strategy in AD.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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