Trends in Molecular Medicine

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Opinion

Adult Hippocampal Neurogenesis in Major Depressive Disorder and Alzheimer's Disease

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Depression and dementia are major public health problems. Major depressive disorder (MDD) and Alzheimer's disease (AD) reciprocally elevate the risk for one another. No effective drug is available to treat AD and about one-third of depressive patients show treatment resistance. The biological connection between MDD and AD is still unclear. Uncovering this link might open novel ways of treatment and prevention to improve patient healthcare. Here, we discuss recent studies specifically on the role of human adult hippocampal neurogenesis (AHN) in MDD and AD. We compare diverse approaches to analyse the effect of MDD and AD on human AHN and analyse different studies implicating the role of human AHN as a potential converging mechanism in MDD and AD.

Highlights

Human AHN is severely depleted in both MDD and AD indicated by reduction of distinct neurogenic markers and hippocampal volume.

Human AHN might be a converging mechanism for MDD and AD, indicating clinical as well as genetic links.

Human AHN might display an interesting therapeutic target to potentially develop novel treatment strategies for MDD and AD.

Challenges of AD and MDD

Mental health disorders are widespread throughout society. Among the most common and most challenging diseases are AD (Box 1) and MDD (Box 2) [1,2]. The risk of developing depression or AD increases with age, thus with the rising number of older adults, AD and depression pose increasing challenges for public health care. Depression and AD are associated. An early-life depression event elevates the subsequent AD risk [3–5], and patients suffering from AD are more prone to develop depression [6,7] and depressed people often have impaired cognition [8–10]. Even though antidepressant treatment can help MDD patients in many cases, a significant proportion of patients do not respond fully to it [11,12], and cognitive impairment may not improve in parallel with the mood symptoms. Even a modest effect in delaying disease onset in subgroups of people at risk for dementia potentially has large societal effects [13], https://www.alzheimers.org.uk/about-dementia/types-dementia/treatments-dementia (see Clinician's Corner). There are many interventions aiming to prevent or delay the onset of dementia, but despite continuous efforts to develop novel therapeutics, there is still no disease-modifying drug available [14]. Therefore, understanding the underlying mechanisms of the depression-induced risk for dementia could help to overcome this problem.

Could Neurogenesis Be a Common Link?

The hippocampus plays a key role in both AD and MDD. In one of its subregions, the dentate gyrus (DG), new neurons are generated throughout life in a process called AHN. The generation of new neurons plays a crucial role in memory and other cognitive functions, as well as the regulation of mood [15–17]. Neurogenesis declines with increasing age, as shown in mice and nonhuman primates [18,19]. In humans, some studies indicate age-related changes to different degrees [20–22], while others do not see an age-related decrease in neurogenesis [23]. Of note, a recent study did not see any age-related changes in intermediate progenitor cells and neurons. Instead, they observed a decrease in quiescent neural stem cells (NSCs) and angiogenesis, resulting in decreased neural plasticity [23]. AHN can be modulated via lifestyle and nutrition [24–26]. Several neuropsychiatric diseases have been associated with aberrations of the neurogenic niche [27], including MDD and AD [17,28–32]. Despite all the evidence, it should be kept in

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Box 1. Alzheimer's Disease

Dementia affects about 50 million people worldwide. About 70% of these people are diagnosed with AD [1]. AD patients typically suffer from memory loss and progressive cognitive decline. Changes in mood and behaviour including anxiety and, in later stages of the disease, impaired motor function can be observed [91]. AD pathology results in synapse dysfunction and loss.

Early-onset AD (EOAD)/familial AD represents 4–6% of all AD cases and usually starts before the age of 65 years. Genetics are the main determinant and heritability of EOAD lies above 90% [93,151]. Genes predictive of EOAD are *APP*, *SORL1*, *PSEN1/2*, and *ABCA7* [93,94]. The more common sporadic/late-onset AD (LOAD) cannot be connected to explicit genetic variations and occurs sporadically, although there is a strong genetic contribution also to LOAD, mediated via several mutations with small effect sizes [95,96]. At least 30% of the risk of LOAD is linked to lifestyle factors, such as low education, hearing loss, depression, cardiovascular disease, metabolic diseases, and head trauma [73].

Even though both amyloid β (Aβ) and Tau deposition are AD hallmarks, it is debated whether they initiate AD pathology [97]. Other factors are considered to contribute to AD pathology. Reactive oxygen species might play a role in neuronal apoptosis [98]. The dysregulation of calcium homeostasis plays a crucial role as well, as it can be linked to excitotoxicity, mitochondrial dysfunction, and apoptosis or necrosis, as well as to increased protein production resulting in increased levels of Aβ and Tau [99–102]. Low levels of the brain-derived neurotrophic factor (BDNF), which plays a crucial role in hippocampus-dependent learning [103,104], have been detected in AD patients during postmortem analyses [105]. Changes in AHN have been linked to AD by multiple studies (see Table 2 in main text) and AHN is among the earlier changes in AD [106].

mind that observed correlations between AHN biomarkers and MDD or AD pathology could potentially result from co-correlations with unknown confounding factors that are yet to be identified.

Nevertheless, human AHN is an interesting target to better understand dysregulation of mood and memory in MDD and AD and might be a converging mechanism by which MDD elevates the risk for AD. Thus, interventions enhancing AHN could help developing novel treatment strategies to tackle

Box 2. Major Depressive Disorder

Depression is characterised by a combination of five or more of the following symptoms: depressed mood, decreased activity, gain/loss of weight, increased/decreased appetite, insomnia/hypersomnia, fatigue, retardation, delusional feelings of guilt and worthlessness, concentration problems, and recurrent suicidal thoughts. MDD is specified by the severity of symptoms, seasonal symptom patterns, psychotic features, and anxiety [107–109]. Genetic and environmental risk factors modify MDD risk. It has been described as a polygenic disorder with a complex and heterogeneous genetic structure with weak effects of each variation itself, but a large cumulative effect promoting disease onset and progression [110], resulting from a combination of genetic and environmental factors [111].

Environmental risk factors for MDD come into play early in life and can have a long-lasting impact. Early traumas, like sexual or physical abuse during childhood, parental separation or witnessing injury or death correlate with a higher incidence of MDD [112]. Physical exercise can reduce depressive symptoms and decrease the risk to develop depression at all [113,114]. Multiple studies indicate a role of nutrition, while heavy smoking, alcohol abuse and the lack of sleep raise the risk of depression [113,115–119].

Multiple mechanisms may contribute to MDD onset and progression. Dysregulation of the **hypothalamic pituitary adrenal axis** might play a role in onset and disease progression [120]. Chronic stress and immune activation are crucial for MDD development [121,122]. Depression has been linked to aberrant noradrenaline signalling [123]. Reduced levels of BDNF correlate with MDD and reduced neural plasticity and neurogenesis [124]. Conversely, BDNF treatment improves depressive symptoms [125].

Many studies have linked MDD to reduced biomarkers of AHN, including reduced numbers of hippocampal GNs and neural stem/progenitor cells, decreased hippocampal and DG volume, and reduced vascularisation of the neurogenic niche [43,46,52]. In turn, SSRI treatment of depressed patients correlates with an increase in those hippocampal biomarkers [43,46,48], indicating a link between AHN and depression.

Tricyclic antidepressants or monoamine oxidase inhibitors have been used to treat depression [126]. SSRIs and SNRIs are most commonly used to treat depressive symptoms [127]. A particularly interesting drug is vortioxetine, which improves cognition in MDD patients. It is believed to inhibit serotonin transporters and acts as a serotonin receptor agonist [127]. Combining pharmacotherapy with psychotherapy often results in better treatment outcomes [128].

Glossary

βIII-Tubulin: microtubule component encoded by *TUBB3* gene, which is almost exclusively expressed in neurons [80].
Braak staging: classification of AD severity according to the progressive spreading of neurofibrillary tangles formed by Tau. The early stages (I/II) refer to pathology which is mainly confined to transentorhinal brain regions. In stages III and IV, the hippocampus and other parts of the limbic system are affected. In stages V and VI, pathology has spread to the neocortex [81].
Bromodeoxyuridine: as it is incorporated into cellular DNA during division, a BrdU-positive cell would have divided after BrdU administration. Often used to measure cell proliferation in hippocampus [82].
^{14}C-method: birth-dating method using carbon isotope. ^{14}C is taken up in cells and is integrated into newly synthesised DNA during cell division. The ^{14}C amount in a cell is dependent on the concentration at the time of the cell division. Presence of different ^{14}C levels in GN DNA demonstrated that new GNs are generated during adulthood.
Calbindin: a calcium-binding protein and marker of mature GNs [80].
Cognitive reserve: concept that accounts for the brain's ability to tolerate or adapt to changes before showing signs of cognitive impairment [83].
Doublecortin: is a microtubule-associated protein expressed in immature neurons and neural progenitor cells [80].
Early-life adversity: includes physical abuse, emotional or psychological abuse, or child neglect [84]. Stress or trauma early in life are large risk factors for depression.
Electroconvulsive therapy: application of small controlled seizures to the brain to improve symptoms in several psychiatric disorders (e.g., depression). Results in changed plasticity, neurophysiological alterations, and changes in neurochemical levels [85].
Genome-wide association study: genome-wide screening of genetic variants in large populations comparing a control group with a group carrying a specific trait to identify variants significantly associated with the trait [86].
Hypothalamic pituitary adrenal axis: hypothalamic signals communicating with pituitary gland and adrenal glands

Key Figure

Dynamics of Adult Hippocampal Neurogenesis (AHN) in Major Depressive Disorder (MDD) and Alzheimer's Disease (AD)

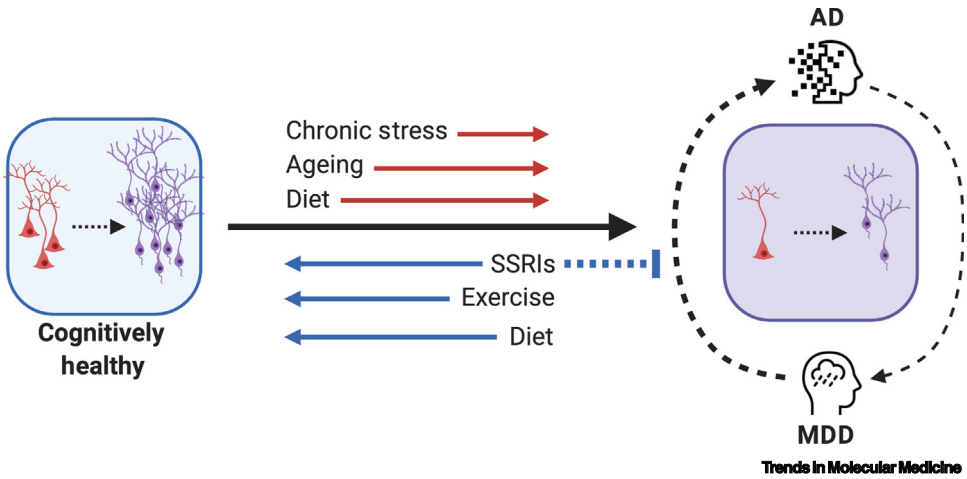

Figure 1. In the hippocampus of a healthy adult, about 700 new neurons are generated every day. Radial glia-like neural stem cells are indicated in red and newborn neurons in purple. Neurogenesis has been proven to be reduced in both MDD and AD. Neurogenesis has been shown to be modulated by many factors, such as exercise, diet and chronic stress both, positively (blue arrows to pointing left) and negatively (red arrows pointing right). Age is one of the biggest risk factors for AD and there is some indication that age correlates with reduced adult hippocampal neurogenesis. Multiple studies indicate that MDD and AD reciprocally elevate the risk for one another, indicated by discontinuous arrows. There is more evidence for MDD to be an AD risk factor than vice versa (indicated by arrow thickness). Treatment with selective serotonin-reuptake inhibitors (SSRIs) might not only increase the rate of AHN back to normal levels (blue arrow pointing left), but also prevent the progression from MDD to AD (broken blue inhibition sign).

both diseases, as well as helping to predict people at increased risk for dementia [16,17,27] (Figure 1, Key Figure). Promising findings have already been made in mouse studies, suggesting that the activity of newly born neurons is crucial to mediate antidepressant effects [33]. Furthermore, a study using an AD mouse model demonstrated that increased AHN improves cognition in AD, while a reduction of neurogenesis exacerbates cognitive impairment [34].

Discovery and Evidence for Human AHN

For decades, it had been believed that no neurons are generated postnatally in the adult brain. Today, we know that the brain is more plastic than previously thought, adapts to environmental changes and can be modulated [16]. In 1965, Altman and Das demonstrated that in adult rats the generation of granule neurons (GNs) continues postnatally by labelling dividing cells in the adult hippocampus DG [35]. More than 30 years later, Eriksson *et al*. provided evidence for AHN in postmortem tissue of patients that received injections of **bromodeoxyuridine** (BrdU, see Glossary) [36]. Further evidence was provided by Spalding and Bergmann. They performed a birth dating approach based on the presence of the isotope **^{14}C** in GN DNA to demonstrate that new GNs are generated during adulthood (~700/day) [21].

The abundance of adult neurogenesis in the human hippocampus has recently been debated. Sorrells *et al.* used **doublecortin** (DCX) and **polysialic acid-neural cell adhesion molecule** (PSA-NCAM) as markers for immature neurons in human adult postmortem brains and found

to regulate glucocorticoid/cortisol levels. Regulates stress response, immune response, and adrenergic and noradrenergic neural circuits [87].
Lewy body dementia: form of dementia that is associated with deposits of a protein called α-synuclein, or so-called Lewy bodies [88].
Nestin: gene encoding for an intermediate-filament protein. Used to label proliferating neural progenitor cells [80].
NeuN: neuronal nuclei antigen encoded by *RBFOX1* gene. Marker for neuronal differentiation [80].
Polygenic risk score: prediction of risk for a certain disease based on cumulative effects of all known associated genetic variations. The effects of those variations are based on data from genome-wide association studies [92].
Proliferating cell nuclear antigen: involved in DNA replication and marker for proliferating cells [80].
Prospero homeobox protein 1: transcription factor specific to hippocampal GNs in the brain [89].
Polysialic acid-neural cell adhesion molecule: marks developing and migrating neurons in the hippocampus [80].
Selective serotonin-reuptake inhibitors: most common form of antidepressant drug (https://www.nhs.uk/conditions/ssri-antidepressants).
Vascular Endothelial Growth Factor A: involved in vascularisation and angiogenesis [90].

almost undetectable levels, questioning the importance of AHN for memory and cognition [20]. Subsequently, contrasting studies provided evidence that AHN persists in adults, even in old age, for example, by demonstrating neurogenic activity in brain samples of donors up to the age of 79 years [23]. Additional studies demonstrated the presence of neurogenesis in the adult hippocampus using markers such as DCX and PSA-NCAM [37,38]. These contrasting findings might be explained by several factors including postmortem interval, method and duration of fixation, as well as different methods of quantification. This has been analysed extensively elsewhere [39]. Altogether, latest studies indicate that AHN in humans persists up into old age.

MDD Is Correlated with Changes in AHN

The hippocampus is involved in mood regulation and changes in neurogenic activity have been associated with MDD. Multiple studies have suggested a reduction of AHN in MDD patients [28,40,41]. Studies on human postmortem brain tissue demonstrated reduced hippocampal volume, decreased numbers of hippocampal GNs, and decreased vascularisation of the neurogenic niche in MDD patients. Vascularisation has been shown to correlate strongly with neurogenesis and increased vascularisation indicates increased levels of neurogenesis as both are regulated by overlapping factors [42,43]. In addition, magnetic resonance imaging (MRI) studies have reported decreased hippocampal volume associated with MDD [44,45]. It should be noted that increased hippocampal volume alone is only an indicator of altered AHN. Volume changes could also originate from other factors including altered numbers of glia cells or differences in cell survival. Therefore, it is important to quantify the numbers of stem cells and newborn neurons to gain confidence about changes in AHN. In contrast, administration of **selective serotonin reuptake inhibitors** (SSRIs) seemed to increase the number of neural progenitor cells (NPCs) in the hippocampus [43,46–48]. A more complete overview of AHN in humans can be found in Table 1. Work on AHN in animal models of depression has been summarised elsewhere [49]. Support for the association of depression and AHN comes from studying cancer patients receiving chemotherapy who develop depressive symptoms. The administered drugs interfere with cell division and, therefore, affect NPC proliferation in the hippocampus [50,51].

A postmortem immunohistochemical analysis of human hippocampal tissue of depressed patients revealed reduced numbers of **NeuN**$^+$ GNs in the hippocampus, with levels dropping to ~30%. This coincided with a decreased volume of the DG of approximately 40% in the anterior DG and 50% in the mid-DG, associated with MDD. Nissl staining and stereological analysis suggested a slight reduction of the mid-granule cell layer (GCL) size. Notably, the differences in GN numbers were reversed upon antidepressant treatment. Both DG and mid-GCL size were enlarged in MDD patients that were treated with SSRIs compared with controls. The number of GNs and the DG size correlated with vascularisation of the neurogenic niche [46]. However, it should be noted that a reduction of GN numbers and changes in hippocampal volume might not necessarily reflect changes in AHN but could originate from other changes such as altered rates of apoptosis. A more recent study reported, in addition to decreased numbers of GNs, reduced numbers of **Nestin**$^+$ cells in the anterior (>80%) and mid (>50 %) DG of MDD patients, indicating a reduction of NSCs [52].

In the same study, the authors investigated the role of AHN in resilience to **early-life adversity** (ELA) [52]. ELA has previously been suggested to increase the risk of developing depression [53]. When comparing healthy people with ELA and MDD patients with ELA, the authors identified significant differences in volume and cell numbers. Both anterior and posterior DG volume and anterior NeuN$^+$ cell counts were increased in tissue from healthy patients with ELA, while for MDD patients with ELA the trend was inverse. The authors concluded that ELA affects AHN. A decrease of DG volume and NeuN$^+$ cells are probably associated with higher susceptibility to stress and that increased AHN after ELA might be a mechanism of resilience [52].

Table 1. Selected Studies on the Role of Human AHN in Depression[a,b]

Disease/cases	Age, year (mean ± SD)	Neurogenic marker	Main results	Refs
One episode of major depression (n = 30), Control (n = 30)	40.6 ± 12.5 40.3 ± 12.6	MRI Hippocampal volume	↓ Hippocampal grey matter (male) ↓ Hippocampal left and right white matter (male and female) Alterations in left/right asymmetry (male and female)	[40]
Depressed suicide subjects (n = 11), Control (n = 11)	36.2 ± 10.1 37.8 ± 11.6	P44/42 MAPK assay Western blot, PCR ERK1/2 levels	↓ P44/42 MAPK activity decreased in hippocampus ↑ MKP2 increased in hippocampus	[130]
MDD (n = 434) Control (n = 379)	N/A N/A	Hippocampal volume (MRI)	Hippocampal volume ↓ in depression	[28]
MDD untreated (n = 31) Control (n = 31)	39.2 ± 11.9 36.7 ± 10.7	MRI Hippocampal volume	No significant changes between control and MDD Within MDD: correlation between MDD severity and level of regional hippocampal atrophy	[131]
Untreated MDD (n = 5) SSRI-treated MDD (n = 4) TCA-treated MDD (n = 3) Control (n = 7)	42 ± 15.8 41.5 ± 17 42.3 ± 16.9 53.9 ± 13	Immunohistochemistry Nestin Ki-67 DG volume	Lower number of progenitor cells in MDD Numbers restored/increased upon treatment with TCA or SSRI: Nestin ↑, Ki-67 ↑ DG volume ↑	[48]
MDD (n = 10) Control (n = 10)	68.7 ± 11.7 68.1 ± 12.5	Immunohistochemistry MCM2 PH3	MCM2 ↓ in MDD PH3 ↔ no response to antidepressant treatment	[30]
MDD (n = 21) Control (n = 21)	41.7 ± 11.0 43.2 ± 10.2 (all subjects were female)	MRI Hippocampal size and shape analysis	Hippocampal atrophy and shape contractions in MDD	[45]
MDD (untreated) (n = 12) MDD (SSRI) (n = 6) MDD (TCA) (n = 6) Control (n = 12)	43.6 ± 13.3 38.8 ± 13.8 46.2 ± 17.1 41.8 ± 14.6	Immunohistochemistry DG volume, capillary area (Nestin/PECAM), No. of NPCs (Nestin/Ki67)	Lower number of NPCs in MDD MDD (SSRI) ↑ NPCs ↑ Capillary area ↑ DG volume MDD (TCA) ↑ NPCs ↑ DG volume	[43]
MDD (untreated) (n = 15) MDD (TCA) (n = 5) MDD (SSRI) (n = 5) Control (n = 17)	51 ± 5 54 ± 10 40 ± 7 44 ± 4	Immunohistochemistry NeuN (GN) GCL volume DG volume	MDD ↓ DG volume ↓ GCL volume ↓ NeuN MDD (SSRI) ↑ GCL volume ↑ NeuN	[46]
MDD (n = 17) Control (n = 17)	41.7 ± 11.0 43.2 ± 10.2	Nissl stain Density of GC, glia, CA2/3 and CA1 cells	MDD vs control ↔ MDD group: ↓ volume and GC numbers with ↑ duration of recurrent/chronic MDD (↑ GC and glia cell number when antidepressants detected postmortem) ↑ CA1, pyramidal neuron density with duration in recurrent/chronic MDD ↑ CA2/3 pyramidal neuron density with age in MDD subjects with no antidepressant detected postmortem ↓ GC density with duration in MDD subjects with no current antidepressant prescription	[132]
Control (n = 57) – self reporting levels of depression (BDI scores) groups: BDI <9 (n = 27) – not depressed BDI >9 (n = 25) – moderate symptoms (no one had a score >29, reflecting severe depression)	19.48 ± 2.05	Neurogenesis-dependent cognition task (pattern separation)	↓ Neurogenesis-dependent memory in BDI >9 group	[62]
MDD (n = 20) nine unmedicated, 11 medicated	47.3 ± 11.5	MRI DG volume	↓ DG volume in MDD – increases upon treatment	[44]

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Table 1. (continued)

Disease/cases	Age, year (mean ± SD)	Neurogenic marker	Main results	Refs
Control (*n* = 27)	48 ± 13.0			
MDD (ECT) (*n* = 15)	54 ± 6	MRI Hippocampal volume, amygdala volume	↑ Volume increase of hippocampus and amygdala after ECT correlating with ↓ depression score	[77]
Mood disorder (MD) (*n* = 17) antidepressant-treated MD [MD (ADT), *n* = 10] benzodiazepine-antidepressant-treated MD (MD – ADT, BZD, *n* = 7) Control (*n* = 18)	51 ± 4.6 34 ± 2.6 57 ± 6.8 46 ± 4.1	Immunohistochemistry DG NPCs (Nestin/Ki67) DG granule neurons (NeuN)	BZD inhibits antidepressant effect on neurogenesis	[47]
MDD (no exercise) (*n* = 38) MDD (exercise) (*n* = 41)	43.8 ± 12.2 38.9 ± 11.7	MRI Hippocampal volume, serum (BDNF, VEGF, IGF-1), verbal memory and Hamilton Depression Rating Scale with 17 items	No changes from intervention, but ↑ right hippocampal volume correlates with ↓ depression score independent of exercise	[133]
MDD (*n* = 10) Control (*n* = 10)	47.3 ± 11.5 48 ± 13.0	Quantitative PCR Telomere length	↓ Telomere length in hippocampus in MDD	[134]
Depression (*n* = 6)	51.3 ± 9.5	MRI Hippocampal grey matter volume	↑ Hippocampal grey matter volume, correlates with ↓depression score, after vagus nerve stimulation for depression treatment	[135]
Dementia (*n* = 41) - untreated (*n* = 13) - treated with SSRIs (*n* = 6) - treated with AChEI (*n* = 12) - combined treatment (*n* = 10) Control (*n* = 15)	N/A 80.92 ± 5.72 80.33 ± 5.82 78.67 ± 4.42 80.1 ± 5.99 80.47 ± 8.48	Immunohistochemistry DCX	↑ DCX with SSRI treatment	[29]
MDD (*n* = 23) Control (*n* = 23)	56 ± 18 56 ± 18	RNA sequencing of DG	↑ Cytokines, inhibitors of angiogenesis, KANSL1 ↓ inflammatory genes, GABBR1	[54]
MDDSui-w/oELA (*n* = 13) MDDSui-wELA (*n* = 13) Control-w/oELA (*n* = 13) Control-wELA (*n* = 13)	41.5 ± 10.9 36.3 ± 20.1 38.5 ± 14.5 36.6 ± 18.5	Immunohistochemistry DG volume GN number (NeuN) NPC number (Nestin) Glia (Nissl stain)	Control-wELA vs Control-w/oELA: ↑ DG volume ↓ NPCs wELA vs w/oELA ↑ GN and Glia MDDSui-w/oELA vs Control-w/oELA: ↓ Anterior and mid-DG GNs ↓ Anterior NPCs ↓ DG volume	[52]
Depressed (*n*= 23), before and after ECT Control (*n* = 8)	50.3 49.25	MRI DG volume (before vs after ECT)	↑ Volume increase in left and right DG, and associated with ↓ in depression scores	[56]
MDD patients (*n* = 220), Treatment with placebo or NSI-149 (40 or 80 mg/day) (3:1:1)	18–60	Several depression scores: primary – MARS: secondary – SDQ, CPFQ, QIDS-SR	Improvement of all depression scores (drug increased hippocampal neurogenesis in model of human foetal hippocampus-derived stem cells and in mouse model)	[55]

[a]↑, increased; ↓, decreased; ↔, unchanged.
[b]Abbreviations: AChEI, acetylcholin-esterase inhibitor; ADT, antidepressant-treated; BDI, Beck Depression Inventory; BZD, benzodiazepine; ERK1/2, extracellular signal-regulated kinase 1/2; IGF-1, insulin-like growth factor 1; MAPK, mitogen-activated protein kinase; MCM2, minichromosome maintenance protein 2; MKP2, MAPK phosphatase 2; PECAM, platelet endothelial cell adhesion molecule; PH3, phosphorylated histone H3; wELA, with ELA; w/oELA, without ELA.

Besides immunohistochemistry analyses, other approaches have been used to investigate the role of AHN in MDD. RNA sequencing of DG tissue from healthy controls and MDD patients identified elevated mRNA levels of inhibitors of angiogenesis in the MDD group [54]. As mentioned earlier, vascularisation and angiogenesis have been correlated with neurogenesis [42,43].

Therefore, impaired angiogenesis might interfere with the neurogenic capacity of the hippocampus. Furthermore, the authors identified inflammatory, as well as neurogenesis-related transcriptional changes in the DG associated with MDD [54].

Several studies suggest that both pharmacological and nonpharmacological interventions may enhance AHN, which not only improves depressive symptoms but also can have beneficial effects on cognition and may reduce the risk of dementia (Box 2 and Clinician's Corner). Pharmacological treatment of patients with NSI-189 phosphate, which has been reported to increase AHN in mice, as well as proliferation of human hippocampal progenitor cells in an *in vitro* model, results in improved depression scores [55]. **Electroconvulsive therapy** (ECT) is used to treat patients suffering from depression. MRI data indicate that ECT results in an increase of hippocampal volume which correlates with improved depression scores [56].

Altered Human Neurogenesis in AD

Multiple studies in rodents [57,58] and humans [27] have investigated the role of AHN in AD pathology. Different studies investigating aberrations of AHN in human AD patients are depicted in Table 2. A detailed immunocytochemistry analysis detected AHN in healthy controls (n = 13) and AD patients (n = 45) up to an age >90 years, elucidating distinct differences between healthy subjects and AD patients [37]. AD patients were grouped according to **Braak stages** to investigate whether increasing AHN depletion correlates with disease progression. DCX^+ neuroblasts were reduced to approximately 60–70% of control levels in less severe AD (Braak stages I–II). As AD pathology progresses (Braak stages IV–VI), DCX levels decreased further to approximately 30–40%. Of all DCX^+ cells, coexpression of PSA-NCAM, **Prospero homeobox protein 1** (PROX1), NeuN, **βIII-tubulin**, or **calbindin** (CB) was reduced, indicating impaired neuronal maturation.

Tobin *et al.* investigated AHN in a cohort up to the tenth decade of life, including cognitively healthy people (n = 6), as well as patients suffering from mild cognitive impairment (MCI), describing memory problems that were not severe enough to be classified as dementia (n = 6), or AD (n = 6) [38]. In contrast to Moreno-Jiménez *et al.* [37], they correlated neurogenic decline with impaired cognitive function rather than progressive Tau pathology. The authors report a reduction of DCX^+/**proliferating cell nuclear antigen** $(PCNA)^+$ cells, reflecting dividing neuroblasts, in the hippocampus of subjects with MCI. Logistic regression analysis demonstrated that reduced numbers of neuroblasts correlate with impaired cognitive performance. The number of neuroblasts is additionally correlated with the functional interaction of SNARE proteins, which are essential for neurotransmitter release. Cognition and the number of $Nestin^+/SOX2^+/Ki67^+$ cells were negatively correlated. The authors speculate that the ratio between the two described cell populations might be relevant in the context of cognitive decline.

Hippocampal gene expression profiles from RNA sequencing in young and healthy aged individuals, and AD patients revealed gene expression differences in AD linked to reduced proliferation and altered vascularisation, decreased neuroprotective functions, and increased cell death [150]. One of many differentially expressed genes was *VEGFA*. **Vascular endothelial growth factor** (VEGF)A directly stimulates NPCs and is important for vascularisation and angiogenesis [59]. It was upregulated during healthy aging but not in AD [150]. As vascularization is essential for the neurogenic niche, a reduction of this process is likely to have a negative impact on neurogenesis [60].

In line with these findings, another study reported differential methylation of genes in hippocampal tissue of AD patients [61]. Many differentially methylated genes could be linked to neural

Table 2. Selected Studies on The Role of Human AHN in AD

Disease/cases	Age, years (mean ± SD)	Neurogenic marker	Main results	Refs
AD (*n* = 7) Control (*n* = 45) – 14 of these were age-matched	13–103	Neuronal loss in different hippocampal subregions (Immunohistology)	Neuronal loss in AD in CA1, hilus and subiculum, most strikingly in CA1 Lower mean cell counts also in CA3-2 and DG yet not significant	[136]
AD Western blot (*n* = 6), Immunocytochemistry (*n* = 5) Controls Western blot (*n* = 6), Immunocytochemistry (ICC) (*n* = 5)	 73.67 80 ± 7 71 70 ± 14	Western blot and immunocytochemistry: NCAM (four isoforms: 195, 185, 145, 120 kDa)	↔ NCAM in AD (all brain regions)	[137]
AD (*n* = 12) Control (*n* = 10)	82.4 ± 10.9 71.1 ± 12.7	Immunohistochemistry and western blot PSA-NCAM	↑ PSA-NCAM in AD (outer molecular layers and inner third of DG) ↑ PSA-NCAM in AD (CA1 subfield sections) ↔ PSA-NCAM in GCL	[138]
Early AD (*n* = 3) Moderate AD (*n* = 3) Severe AD (*n* = 3) Control (*n* = 7)	76.67 79 77.33 35.4	Western blot DCX PSA-NCAM NeuroD Tuc-4 Calbindin NeuN	Western blot ↑ DCX, PSA-NCAM, Tuc-4 and NeuroD in AD hippocampus ↔ Calbindin, D28K and NeuN	[139]
AD (*n* = 5) Control (*n* = 4)	74.8 66	IHC DCX Tuc-4	Immunohistochemistry ↑ TUC4 and DCX in GCL in AD.	[139]
Cases (*n* = 17) - Dementia (*n* = 8) - Controls (*n* = 11)	71–102	Immunohistochemistry MCM2 Ki-67 PCNA	↑ MCM2 in glia in CA1 in higher Braak groups ↑ proliferation markers in higher Braak groups	[140]
AD (*n* = 7) Control (*n* = 7)	82.50 ± 4.97 79.67 ± 3.93	Immunocytochemistry Msi-1 Nestin GFAP	↑ Nestin in SVZ in AD. ↔ Nestin in ependymal layer ↓ Msi-1 in SVZ in AD. ↔ Msi-1 in ependymal layer ↔ GFAP in subventricular zone (SVZ)	[141]
AD (*n* = 9) Control (*n* = 10)	66.2 ± 2 67.1 ± 2.3	Immunohistochemistry DCX GFAP Ki67	↑ Ki67 in CA1-3 in AD (due to increases in glia-rich and blood vessel-rich areas) ↑ GFAP in DG in AD ↔ DCX in AD	[142]
AD (*n* = 14) Control (*n* = 15)	79.4 ± 10.9 83.6 ± 7.4	Immunohistochemistry and in situ hybridisation MAP2a/b/c	↓ MAP2a/b in AD DG. ↔ MAP2c	[31]
Early/moderate AD (*n* = 7) severe AD (*n* = 7) Control (*n* = 5)	86.1 ± 1.7 80.0 ± 1.9 87.0 ± 4.6	Immunocytochemistry DCX SOX2 BMP-6 qRT-PCR BMP-6	↓ DCX and SOX2 in severe AD ↑ BMP-6 in AD	[32]
AD (*n* = 20) Control (*n* = 21)	81.2 ± 7.0 80.9 ± 8.5	Immunohistochemistry Msi-1 Nestin DCX PSA-NCAM β-tubulin	↓ Msi-1 in SGZ and GCL in AD (negative correlation with Braak staging) ↔ Msi-1 in SVZ. ↑ Nestin in SVZ, SGZ and GCL in AD (correlation with Braak staging) ↑PSA-NCAM in SGZ and GCL in AD (correlated with Braak staging). ↔ in PSA-NCAM in SVZ. ↑DCX in GCL in AD. ↔ β-III-tubulin in AD.	[143]
AD (mild – moderate) (*n* = 66) Control (*n* = 104)	76.6 ± 7.5 76.9 ± 4.1 (all participants were female)	CDR System pattern separation task, ApoE ε4 genotype and cerebrospinal Aβ42	Presence of ApoE ε4 genotype and increased Aβ42 levels correlated with worse performance in difficult pattern-separation tasks	[144]

Table 2. (continued)

Disease/cases	Age, years (mean ± SD)	Neurogenic marker	Main results	Refs
AD (*n* = 10) Control (*n* = 9)	58–79 58–79	Immunohistochemistry Ki67 Calretinin SOX2	↑ Ki67 and Calretinin in SGZ of DG of AD ↔ SOX2 in AD	[145]
Braak stage 0–II (*n* = 12, dementia *n* = 3) Braak stage III–IV (*n* = 11, dementia *n* = 5) Braak stage V–VI (*n* = 5, dementia *n* = 5)	80.3 ± 8.4 88.9 ± 8.2 86.8 ± 5.3	Immunohistochemistry Nestin DCX PCNA HuC/D GFAP	↔ Nestin in DG. ↓ HuC/D in DG in Braak V-VI. ↓ GFAP in DG in Braak III-IV ↑ GFAP in DG in Braak V-VI ↑ DCX in DG in higher Braak stages ↔ all markers in SVZ and ECL	[146]
MCI (*n* = 3) Symptomatic AD (*n* = 6) Non-demented AD pathology (*n* = 4) Control (*n* = 4)	74 to >89 67 to >89 >89 74 to >89	Immunocytochemistry NSC numbers in dissected DG miRNA qRT-PCR from dissected DG	↑ $SOX2^+$ NSCs in nondemented AD compared with symptomatic AD ↓ Neurogenesis-regulating miRNA in nondemented AD compared with symptomatic AD	[147]
Significant memory concerns (*n* = 94) Early mild cognitive impairment (*n* = 280) Late mild cognitive impairment (*n* = 512) AD (*n* = 310) Control (*n* = 367)	71.77 ± 5.65 71.14 ± 7.26 73.52 ± 7.65 74.65 ± 7.79 74.59 ± 5.57	Gene-based association analysis ADORA2A, MRI Hippocampal volume	ADORA2A variant (rs9608282) associated with increased hippocampal volume, lower Tau levels and improved memory. AD patients with this variant also higher hippocampal volume	[148]
AD (Braak V/VI) (*n* = 5) Control (*n* = 39)	74–89 gestational week 13–72 years	Immunohistochemistry $Nestin^+$, $GFAP^+$/$Vimentin^+$, $GFAP^+$/$PAX6^+$, $GFAP^+$/$PAX6^-$ (semi quantitative)	AD similar to controls, less contact between $Nestin^+$ or $GFAP^+$ with blood vessels. More GFAP than Nestin in AD cases	[149]
AD (*n* = 18) Young control (*n* = 17) Aged control (*n* = 21)	70–99 20–50 70–99	Hippocampal gene expression profiles	Altered hippocampal gene expression in AD, associated with: - possible vascular dysfunction - altered proliferation and cell death - altered neuroprotective function	[150]
AD (*n* = 45) *Braak I (n = 5)* *Braak II (n = 3)* *Braak III (n = 4)* *Braak IV (n = 4)* *Braak V (n = 13)* *Braak VI (n = 16)* Control (*n* = 13)	52–93 43–87	Immunocytochemistry DCX PSA-NCAM	↓ DCX: decreases with each Braak stage ↓ PSA-NCAM	[37]
MCI (*n* = 6) AD (*n* = 6) Control (*n* = 6)	86–95 85–99 79–93	Immunocytochemistry DCX DCX/PCNA Nestin/Sox2/Ki67 Hippocampal Volume	↓ DCX/PCNA in MCI (correlates with lower cognitive score and less interaction of presynaptic SNAREs)	[38]
AD (*n* = 26) Control (*n* = 12)	59–96 19–88	ChIP–qPCR Differentially methylated positions (DMPs)	AD-related DMPs in hippocampal committed NPCs and neurogenesis-related genes (includes homeobox transcription factors)	[61]

[a] ↑, increased; ↓, decreased; ↔, unchanged.
[b] Abbreviations: MAP2, microtubule-associated protein 2; BMP-6, bone morphogenic protein 6; CDR, clinical dementia rating; PAX6, paired box 6; ADORA2A, adenosine A2A receptor; qRT-PCR, quantitative real-time PCR; ChIP-qPCR, chromatin immunoprecipitation quantitative PCR; SNARE, soluble N-ethylmaleimide-sensitive-factor attachment receptor.
[c] This table has been adapted and updated from [80].

differentiation, reflecting alterations in hippocampal neurogenesis. This association is strong, even when compared with the usual AD-associated pathways (apoptosis, autophagy, inflammation, oxidative stress, and mitochondrial or lysosomal dysfunction) suggesting a significant role of AHN in AD, even in comparison with more commonly associated pathways.

AHN as a Potential Mediator of the Increased Risk of AD Associated with MDD

Given that AHN might be altered in both MDD and AD, AHN might not only be correlated with, but also possibly mediate the increased risk of AD in people with a history of MDD. Few studies have explored this possible interaction, but a postmortem analysis of human brain tissue suggests that treatment of depression using SSRIs is associated with increased numbers of DCX^+ cells in patients with **Lewy body dementia**, indicating increased neurogenic activity. Moreover, patients receiving this treatment displayed less cognitive decline. In fact, increased levels of DCX correlated with better cognitive scores [29]. These findings support the hypothesis that antidepressant induced enhanced AHN may both improve mood and potentially prevent neurodegeneration and preserve memory. Notably, depressed patients perform worse in hippocampus-dependent cognition tasks compared with a nondepressed group, indicating that the hippocampus does link mood and memory in depression [62].

A recent study analysed several MDD risk loci for association with AD by using **genome-wide association studies** (GWASs) summary statistics, mRNA expression analyses of MDD risk genes in AD patients and murine AD models, as well as sequencing of whole coding regions of MDD risk genes in 107 Han Chinese patients with AD [63–65]. Some genes could be associated with both MDD and AD, and some of these are highly expressed in the hippocampus. For instance, *SORCS3* could be associated with an increased pathological burden in the hippocampus as it is involved in the processing of the amyloid precursor protein (APP), potentially affecting AHN [66]. Another gene overlapping between MDD and AD is *MEF2C*, which has been linked to memory and synapse regulation and *MEF2C* knockdowns have been associated with impaired neuronal differentiation and maturation, processes that are relevant to AHN [67–69].

Furthermore, **polygenic risk scores** (PRSs) of genetic MDD risk variants in nondepressed people suffering from MCI have been associated with decreased hippocampal grey matter volume and are predictive of the conversion from MCI to AD. Following up with a hippocampus-specific analysis of genes involved in the PRS, the data reveal that genes that are altered are involved in processes like axon guidance, anatomical structural morphogenesis, neuron projection, and cellular development [70].

These studies strengthen the hypothesis of a genetic or mechanistic link between MDD and AD and indicate that AHN could indeed be a mechanism by which MDD increases the risk for AD or results in earlier onset, possibly due to a reduced **cognitive reserve**. However, more studies are needed to provide more evidence for this hypothesis.

Comparative Analysis of Neurogenic Reduction in AD and MDD

The process of AHN involves several stages, which can be differentiated by expression of different markers, ranging from radial glia (RG)-like NSCs over transiently amplifying NPCs and neuroblasts to immature and mature postmitotic neurons (Figure 2A). Using immunocytochemistry and immunohistochemistry analyses of human postmortem brain tissue, two recent studies investigated neurogenic changes in AD [37], and the decline of AHN in MDD [52] (Figure 2B). Notably, many of the findings complement each other. DCX^+ cells, which are probably representing neuroblasts, as well as early postmitotic neurons are reduced [37]. Nestin, labelling NSCs and early transiently amplifying NPCs, and NeuN a marker for early postmitotic and more mature

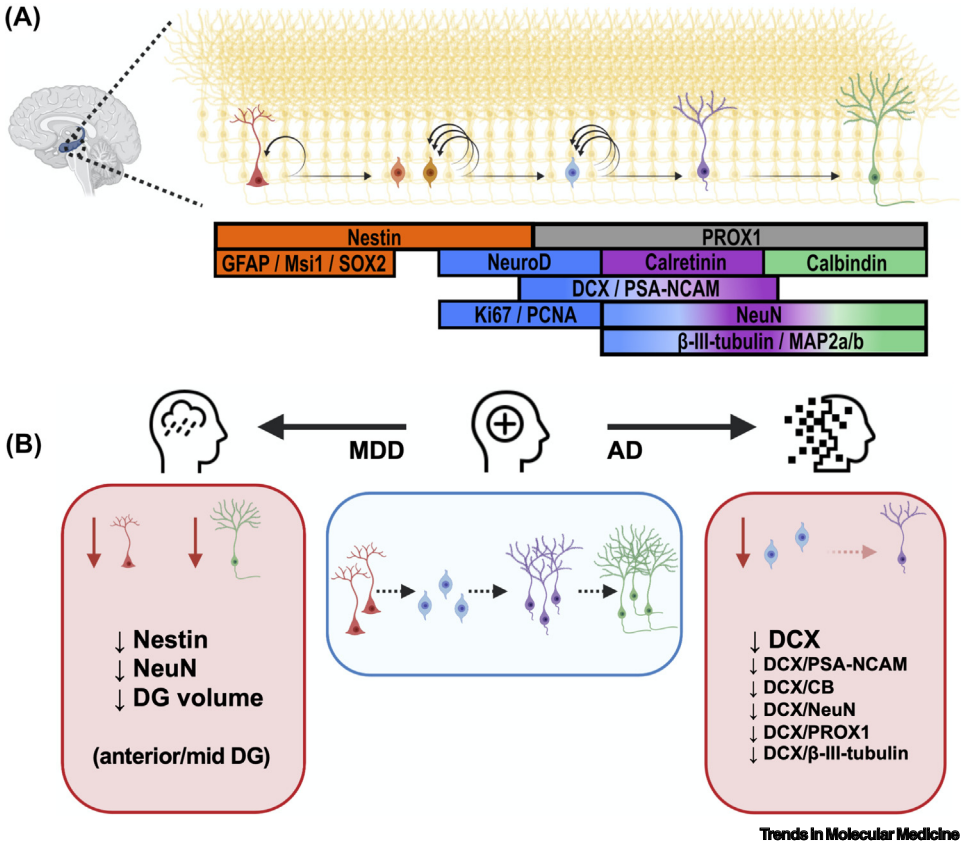

Figure 2. Stages of Human Adult Hippocampal Neurogenesis (AHN) and Immunocytochemical Analysis in Major Depressive Disorder (MDD) and Alzheimer's Disease (AD). (A) Generation of new neurons takes place in the subgranular zone (SGZ) of the dentate gyrus (DG) which harbours the type I radial glia-like neural stem cells (RGL-NSCs, red). RGL-NSCs divide sporadically and give rise to the rapidly proliferating type II a/b transient amplifying neural progenitor cells (light red/orange). They give rise to type III neuroblasts (blue), which are still proliferating. Once they exit the cell cycle, they form immature neurons in the granular layer (purple). During the early postmitotic phase, they are excitable by GABA, regulating dendritic maturation and synaptic integration until they have properly matured (green) and connected to the surrounding signalling network (yellow) [129]. Below, corresponding markers are indicated in matching colours to highlight stage specificity. Prospero homeobox protein 1 (PROX1) (grey) marks the granule neuron lineage, instead of specific stages (Adapted, with permission, from [80]). (B) Major findings on AHN alterations in MDD or AD. MDD is associated with decreased levels of Nestin$^+$ and NeuN$^+$ cells, expressed by neural stem cells and mature neurons, respectively, as well as with a lower dentate gyrus (DG) volume, especially in the anterior and mid-DG. AD is strongly associated with decreased doublecortin (DCX)$^+$ cells, representing progenitors or neuroblasts. DCX$^+$ cells colabelled with other markers [polysialic acid-neural cell adhesion molecule (PSA)-NCAM), DCX/CB, DCX/NeuN, DCX/PROX1, DCX/βIII-tubulin), are decreased, indicating impaired differentiation from neuroblasts into immature neurons. Abbreviations: CB, calbindin; GFAP, glial fibrillary acidic protein; MAP2a/b, microtubule-associated protein a/b; Msi1, musashi-1; NeuN, neuronal nuclear antigen; PCNA, proliferating cell nuclear antigen; SOX2, SRY-box transcription factor 2.

GNs are also reduced [52]. Furthermore, DG volume and GCL size are reduced [52], although changes in volume are not proof for altered AHN and could originate from changes in glial cell counts, altered apoptosis, and altered vascularisation, etc. While the results from both studies indicate a decrease in the presented markers, supporting the hypothesis of AHN dysregulation in neuropsychiatric diseases, neither of them assessed the whole neurogenic trajectory completely. Moreover, the use of different markers makes it difficult to compare findings, especially quantitatively, among different studies.

A reduction of NeuN$^+$ cells only might not necessarily mean that fewer new neurons are born, and increased rates of apoptosis would lead to a similar result. Only the addition of Nestin as a second marker increases confidence that decreased NeuN$^+$ cells might be a result of a reduction of Nestin$^+$ NSCs/NPCs. Colabelling of DCX with a second marker for postmitotic cells (NeuN, PSA-NCAM, β,III-tubulin, CB or PROX1) gives more robust data to demonstrate a reduction of neuroblasts and early postmitotic neurons. While this gives evidence for a reduction of neuroblasts and early postmitotic cells, it does not provide information on the NSC pool. Therefore, none of the aforementioned studies draw a complete picture of the neurogenic trajectory. It might be useful, to define distinct sets of markers to label all stages of AHN in order to create findings that are comparable among different studies. Furthermore, analysing for all stages of AHN gives a better impression of where neurogenesis might be disturbed.

When looking at changes of AHN in MDD, different DG subregions demonstrate MDD related changes predominantly in the anterior- and mid-DG [52]. The more prominent reduction of neurogenic activity in anterior regions is in line with previous studies suggesting that the anterior (ventral in mice) DG is more involved in mood regulation, while the posterior part (dorsal in mice) shows stronger links to cognition [71]. A similar differentiation into subregions in the context of AD would be interesting to investigate whether changes might be more prominent in the posterior DG.

Concluding Remarks

In our ageing population, depression and dementia become increasingly prominent and present major challenges for society. The role of depression as a possible risk factor for dementia and the overlap of MDD and AD have been under debate. Here, we focused on human studies demonstrating the role of AHN in MDD and AD, as well as some indications that hippocampal neurogenesis might display a converging link between those two diseases.

Although use of antidepressants improves cognition in patients with Lewi body dementia [29], this does not necessarily mean that the same applies to AD. We propose to further study whether the treatment of depression that prevents or delays the onset of cognitive decline and AD involves AHN (see Outstanding Questions). Postmortem analyses of neurogenic decline in MDD or AD present findings that are complementary, but difficult to compare. One way to create a more comprehensive view on AHN in depression and dementia would be to define a commonly used set of markers that labels all different stages of neurogenesis in the human brain. This would allow a comparison of findings across different studies and disorders and enable better interpretations regarding the role of AHN. Furthermore, postmortem analyses only depict a screenshot of AHN which is a very dynamic process. While recent studies indicate a reduction in neurogenesis, it cannot be proven with certainty, as not all stages of AHN are visualised in either of those studies. AHN is a dynamic process; developing a live model for direct assessment of AHN could contribute to understanding its role in MDD and AD. Some *in vitro* models of human hippocampal neurogenesis already exist; for example, using human induced-pluripotent-stem-cell-derived GNs [72]. Similar models could be used to investigate the effect of hippocampal neurogenesis in MDD and AD.

Genetics could provide further insight into the overlap of AD and MDD. Multiple GWASs have looked at genetic alterations in MDD or AD [63,64] and identified overlaps between both diseases [65]. A combination of these data with cellular assays could provide further functional understanding of AHN as a possible converging mechanism.

Clinician's Corner

Depression is widespread among older people and often accompanied by cognitive impairment which can progress to dementia [73]. Especially in patients with late-life depression, it can be difficult to decipher whether cognitive impairment is a side effect of depression, or whether it is a symptom of dementia/AD [74,75].

Antidepressants may improve cognitive function in the short term, but it is unclear if they have a protective effect against dementia.

Hippocampal neurogenesis can be increased by certain antidepressants and nondrug interventions, such as diet or exercise [24,76], but its role in depression-induced cognitive decline in elderly people is not clear. SSRIs have previously been shown to improve depressive symptoms, as well as to increase hippocampal neurogenesis. Similar findings have been reported after ECT [56,77]. The compound vortioxetine has been reported to improve cognition in depressed patients [78].

Cognitive training improves cognition but its potential in treating depression-induced cognitive decline is unknown [79].

Altogether, AHN is crucial for the manifestation of new memories and cognitive function, as well as the regulation of mood. If disturbed, it can have severe consequences for mental health. AHN has been shown to be involved in AD pathology and to play a role in MDD. The human studies presented here provide some evidence that AHN is involved in both disorders. Even though current findings do not prove a direct link between AD and MDD, they suggest that AHN might be a possible crossroad. In the long run, this opens up a new avenue for potentially preventing the onset of AD and other dementias.

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Outstanding Questions

Can immunocytochemical postmortem analyses of human brain tissue be more comparable across different laboratories? Recently, immunocytochemical analysis has undergone great advancements. It has also become clear that postmortem delay and fixation methods greatly influence the analysis. Moreover, it would be interesting to analyse the whole neurogenic trajectory including specific markers for all stages (RG-like NSCs, NPCs/neuroblasts, and newborn neurons). This would make the comparison of neurogenic changes amongst different studies more comparable.

How strongly do genetics support the concept of AHN as a biological link between MDD and AD? Some studies now indicate that GWAS-identified MDD risk genes might be involved in AD. How strong is the genetic overlap between MDD and AD? If different genes are affected, are they involved in overlapping cellular mechanisms?

Is depression a risk factor for AD, or is it rather a common early symptom which arises prior to any cognitive decline? Depression, often occurs in association with AD. However, it is debated, whether depression itself promotes the progression to AD, or whether it is just a symptom of AD, as it not only occurs prior to it, but also can occur later during the disease.

Can cellular models utilising living human cells/tissue be used to model genetic alterations in MDD and AD to gain further mechanistical insight? Which information could be gained from using patient-derived cell lines or isogenic lines looking at selected mutations?

Do MDD and AD affect multiple stages of AHN, or do they interfere at selective timepoints of neurogenesis? Are the stages of neurogenesis affected differently in MDD and AD? Is there regional specificity? Studies on depression indicate a stronger involvement of the anterior DG. Is in AD the posterior DG more affected?

Could AHN be a novel therapeutic target to treat MDD and AD? For instance, would an increase of AHN in patients suffering from late-life depression prevent their progression to dementia?

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