Neurogenesis in aging and age-related neurodegenerative diseases

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Abstract

Adult neurogenesis, the process by which neurons are generated in certain areas of the adult brain, declines in an age-dependent manner and is one potential target for extending cognitive healthspan. Aging is a major risk factor for neurodegenerative diseases and, as lifespans are increasing, these health challenges are becoming more prevalent. An age-associated loss in neural stem cell number and/or activity could cause this decline in brain function, so interventions that reverse aging in stem cells might increase the human cognitive healthspan. In this review, we describe the involvement of adult neurogenesis in neurodegenerative diseases and address the molecular mechanistic aspects of neurogenesis that involve some of the key aggregation-prone proteins in the brain (i.e., tau, Aβ, α-synuclein, …). We summarize the research pertaining to interventions that increase neurogenesis and regulate known targets in aging research, such as mTOR and sirtuins. Lastly, we share our outlook on restoring the levels of neurogenesis to physiological levels in elderly individuals and those with neurodegeneration. We suggest that modulating neurogenesis represents a potential target for interventions that could help in the fight against neurodegeneration and cognitive decline.

Keywords

Neurogenesis; neurodegeneration; aging; dentate gyrus; hippocampus; memory

1. Introduction

It is known that aging is a major risk factor for neurodegeneration, and that the most common neurodegenerative diseases are observed in the elderly (Hou et al., 2019). Despite ongoing research and progress in the field, cures for such chronic afflictions have not yet been found. Hence, their burden on society is very high and, as the population ages and lifespans lengthen, it is expected to increase (Dorsey et al., 2013; Zahra et al., 2020). Some researchers have suggested that a decline in the function of the central nervous

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system (CNS) is one of the main hallmarks of aging in mammals (Hayano et al., 2019). As such, this decline may be susceptible to interventions that attempt to target aging itself, simultaneously delaying or preventing other diseases as well (extending healthspan). One attractive theory is that the decline in brain function with age is caused by a loss in stem cell number and/or activity over time, and that interventions that delay or reverse aging in stem cells might extend human lifespan and healthspan (Schultz and Sinclair, 2016). In the brain, those stem cells are neural stem cells (NSCs), and the process of generating new neurons is called neurogenesis.

1.1. Neurogenesis

Does adult neurogenesis exist in humans?—The discovery of neurogenesis in the adult mammalian brain occurred by serendipity in the 1960s by Joseph Altman and Gopal Das (Altman, 2011, 1962; Altman and Das, 1965). The finding was mostly neglected through the 1970s and 1980s (Altman, 2011), and in 1985, a widely-cited paper denied the possibility of the phenomenon in primates (Rakic, 1985). In the late 1990s it was confirmed that neurogenesis occurs in adult macaques (Gould et al., 1999) and humans (Eriksson et al., 1998), but the controversy remains. For example, recent studies directly contradict each other, with one showing that adult hippocampal neurogenesis (AHN) drops sharply in children to undetectable levels in adults (Sorrells et al., 2018), and the other showing that AHN persists throughout aging (Boldrini et al., 2018). Many questions remain unanswered, and while some studies supported Sorrells et al.'s study (Seki et al., 2019), others claimed that it was not optimized for detecting neurogenesis (due to postmortem delay, long fixation period and other factors). They argued that the findings by Boldrini et al. are more in line with the current body of knowledge that supports the existence of AHN in humans (Kempermann et al., 2018; Lucassen et al., 2020). Moreover, a recent study by Moreno-Jiménez et al. (2019), that was methodically optimized for detecting neurogenesis (through tissue fixation, autofluorescence quenching, epitope retrieval, antibody selection and selection of subjects with a short post-mortem delay), was able to detect immature neurons in the dentate gyrus (DG) of 13 healthy individuals up to the ninth decade of life (Flor-García et al., 2020; Steiner et al., 2019). However, some researchers claim that the number of newborn neurons in those studies is likely to be overestimated, as the expression of putative progenitor cell and immature neuron markers does not present definitive evidence for adult neurogenesis. According to their critique, these markers can be re-expressed in mature adult neurons through the process of "dematuration", a phenomenon in which mature neurons dedifferentiate to a pseudo-immature status and re-express the molecular markers for neural progenitor cells and immature neurons (Hagihara et al., 2019). A recent pair of "Dual Perspectives" articles argue for and against the existence of AHN, but both agree that further in-depth studies of AHN are extremely important (Moreno-Jiménez et al., 2021; Sorrells et al., 2021). Lastly, a recent study utilizing single-nucleus RNA sequencing to thoroughly profile cells from the hippocampal-entorhinal system showed that AHN is virtually absent from adult human donors (Franjic et al., 2021). Also, it is possible that higher AHN was not detected due of the postmortem delay, the insufficient number of cells profiled (~139k), or other confounding factors. Hence, the controversy still remains and, until neurogenesis has been measured more directly (e.g., after technical advances in magnetic resonance spectroscopic imaging) and until the cells are profiled even more

thoroughly, the studies cited above (Boldrini et al., 2018; Elena P. Moreno-Jiménez et al., 2019; Spalding et al., 2013) are the strongest proof to date that neurogenesis persists in humans, even in old age. While a study using magnetic resonance imaging provided evidence for NSCs *in vivo* (Manganas et al., 2007), others question if the signal is specific to NSCs (Ramm et al., 2009) and note that the method is unable to differentiate hippocampal sub-regions (Boldrini et al., 2018). We also note that even if AHN is virtually absent in aged humans, it may still be possible to reactivate or stimulate it with various interventions.

Where does adult neurogenesis occur?—Neurogenesis is considered to occur in two so-called neurogenic areas of the brain: the subgranular zone (SGZ) of the hippocampal DG and the subventricular zone (SVZ) of the lateral ventricles (Hagg, 2009). While there have been reports of adult neurogenesis in "noncanonical" sites of the mammalian brain, such as the neocortex of primates (Gould et al., 1999), the cerebellum of rabbits (Ponti et al., 2008), the amygdala of mice (Jhaveri et al., 2018) and the striatum of humans (Ernst et al., 2014) (summarized in (Feliciano et al., 2015)), we will mostly focus on the hippocampus, as a consensus hasn't been reached in regard to neurogenesis occurring in other areas (and in which species), much less the dynamics of the process. For instance, while immature neurons (neuroblasts) migrate from the SVZ to the olfactory bulb (OB) through the distinct rostral migratory stream (RMS) in rodents (Hagg, 2009), the existence and configuration of the adult RMS in humans remains highly debated (Arellano and Rakic, 2011; Bergmann et al., 2015; Sanai et al., 2011), just like the existence and the quantity of postnatal neurogenesis in the human OB (Bergmann et al., 2012; Lledo and Valley, 2016). Unlike those areas, neurogenesis in the hippocampus has been studied to a much greater extent, with rodent studies showing that the exposure to enriched environment has a beneficial effect on both neurogenesis and aging (van Praag et al., 2000), while models of aging-related neurological diseases such as AD and PD show impaired AHN, which could be one of the mediators of their respective pathologies (Toda et al., 2019).

Age- and neurodegeneration-dependent dynamics of neurogenesis—The hippocampus is a major brain region involved in memory, emotional processing, and vulnerability to stress, and is one of the most severely affected areas in AD (Brown, 1999; Dhikav and Anand, 2012). In fact, a defining feature of AD is the accumulation of tau and amyloid-β (Aβ) (Bloom, 2014), which begins in the entorhinal cortex, a major gateway to the hippocampus (Maass et al., 2015), and spreads to the cortex and the hippocampus itself (Khan et al., 2014; Toda et al., 2019). Two recent studies found that the number and maturation of new-born neurons in the hippocampus progressively declined as AD advanced and suggested that this decline might promote cognitive deficits or exacerbate them (Elena P Moreno-Jiménez et al., 2019; Tobin et al., 2019). Therefore, the levels of AHN could be considered as one of the potential biomarkers for neurodegenerative diseases such as AD (Lopez-Toledano et al., 2010). To utilize this biomarker in humans, besides obviously making the measurement less invasive, we would first need to determine the physiological range of AHN in healthy subjects, especially considering how it depends on factors like age, exercise and caloric intake (Levenson and Rich, 2007; Van Praag, 2008). Age-related dynamics of AHN across species have been reviewed elsewhere (Kozareva et al., 2019). We will just mention its dynamics in humans, which has been estimated through ^{14}C levels

in the genomic DNA of hippocampal neurons. The model estimated that around 700 new neurons are added in the hippocampus per day (0.004% of DG neurons), which corresponds to an annual turnover of 1.75% of the neurons within the renewing fraction, with a modest age-dependent decline (Spalding et al., 2013). However, it should be noted that the same study reported that the generation of new neurons in the DG does not keep up with the neuronal loss with age, and that the half-life of these newborn neurons in the renewing fraction is 10× shorter (7.1 years) than in the non-renewing fraction. It is not yet known whether just restoring the AHN to physiological levels would confer a therapeutic benefit for cognitive healthspan, or if further increase would be necessary. We will discuss this in more detail in the conclusion.

1.2. Functional relevance of newborn hippocampal neurons

The functional relevance of newborn hippocampal neurons has been implicated in many processes, such as resilience to and remission from stress, pattern separation, memory formation and learning, as well as in neurological disorders such as AD and PD (Anacker et al., 2018; Culig et al., 2017; Gonçalves et al., 2016; Höglinger et al., 2004; Elena P Moreno-Jiménez et al., 2019). As the latter will be described in more detail in section 2 of this review, we will now describe the data supporting the other roles of newborn neurons.

Stress—Animal studies showed that both stress and exposure to stress hormones (glucocorticoids) decrease the generation of hippocampal neurons and increase cell death (Culig and Belzung, 2016; Gould et al., 1998, 1992, 1991, but see Brunson et al., 2005), while chronic treatment with different classes of antidepressants has an opposite effect and increases neurogenesis (Malberg et al., 2000). Early-life stress in rodents has a negative effect on AHN (Criado-Marrero et al., 2020b; Naninck et al., 2015), hippocampal-dependent learning and memory (Rocha et al., 2021; Tzanoulinou et al., 2020) as well as on the later risk for cognitive impairments and AD (Hoeijmakers et al., 2017; Lesuis et al., 2018). In human studies, it has also been shown that smaller hippocampi constitute a risk factor for the development of stress-related psychopathology (Gilbertson et al., 2002). The level of AHN and/or the number neural progenitor cells decrease in patients with MDD and increase after treatment with antidepressants (Boldrini et al., 2012, 2009; Lucassen et al., 2010). A causal relationship between antidepressant treatment and newborn neurons was established, demonstrating that AHN is *required* for many of the behavioral effects of these drugs (Santarelli et al., 2003). A more nuanced picture emerged with further experiments showing that there are neurogenesis-dependent and -independent effects of antidepressants (David et al., 2009; Surget et al., 2008). Finally, gain-of-function studies where researchers were able to inducibly increase neurogenesis by inhibiting neuronal cell death (apoptosis) in transgenic mice established a role for newborn neurons in both resilience to and remission from stress (Culig et al., 2017; Eliwa et al., 2021; Hill et al., 2015). Another function of the hippocampus related to mood and stress is the regulation of the hypothalamic–pituitary–adrenal (HPA) axis, the main neuroendocrine system in mammals that provides a rapid response and defense against stress (Spiga et al., 2014). The inhibitory hippocampal regulation of the HPA axis is attenuated by exposure to stress (Mizoguchi et al., 2003; Surget et al., 2011), and newborn hippocampal neurons are required for appropriately maintaining this regulation (Schloesser et al., 2009; Snyder et al., 2011),

which has implications for stress reactivity and mood disorders such as major depressive disorder (MDD). However, the exact role that newborn neurons play in HPA regulation and vulnerability to stress is not yet resolved (Lucassen et al., 2013), and has been discussed elsewhere (Culig et al., 2017).

Pattern separation—Pattern separation, defined as the process of transforming similar input patterns into less similar output patterns, is suggested to be crucial for discriminating memories that are similar in content and is performed in the DG (Lacy et al., 2010; Treves et al., 2008). Animal studies show that ablation of AHN impairs pattern separation (Clelland et al., 2009; Luu et al., 2012; Tronel et al., 2012), while increasing AHN is sufficient to improve it, regardless of whether the increase is obtained in a specific manner by genetically enhancing the survival of new neurons (Sahay et al., 2011) or through non-specific interventions such as enriched environment (Clemenson et al., 2015b). Behavioral paradigms to study pattern separation in animals, such as the location discrimination task, contextual fear conditioning and the newly developed spontaneous location recognition task, have been described elsewhere (Reichelt et al., 2021) and a meta-analysis of behavioral data supports the conclusion that AHN plays an important role in pattern separation (França et al., 2017).

Human studies that used (high-resolution) (f)MRI have provided compelling evidence for the involvement of DG in pattern separation (Bakker et al., 2008; Berron et al., 2016; Dillon et al., 2017; Hanert et al., 2019). Other indirect evidence has been summarized elsewhere (Lucassen et al., 2020), and includes results from tasks for measurement of pattern separation specifically in human DG (Stark et al., 2019), linking improved performance in it with an fMRI signal in the DG, indirectly supporting the idea that this function of newborn neurons is conserved in humans. DG dysfunction and pattern separation impairments during normal aging have been reported in non-human primates and humans (Small et al., 2004; Toner et al., 2009; Yassa et al., 2010). Further support came from a study that examined the relationship between performance in pattern separation tasks with lifestyle factors correlated with neurogenesis (aerobic exercise and high levels of stress) (Déry et al., 2013). The authors reported opposing effects of aerobic exercise (known to upregulate neurogenesis) and depression (which is associated with reduced DG cell proliferation and/or survival) on memory interference. However, because both of those factors have widespread effects, it is possible that one or more additional variables were affected by exercise and stress, which themselves could have caused or contributed to the observed effects. The exact mechanism through which newborn cells enhance pattern separation is still not known (Gonçalves et al., 2016). There are various difficulties in studying pattern separation, one of them being that to rigorously demonstrate that the DG is involved in pattern separation, it would be necessary to have the knowledge of DG's inputs and outputs. While a rigorous test of this kind is lacking *in vivo*, a direct experimental demonstration of multiple forms of temporal pattern separation in DG brain slices has been provided recently (Madar et al., 2019a, 2019b). Likewise, due to the difficulties associated with measuring AHN *in vivo*, the direct confirmation of the role of newborn neurons in pattern separation is not confirmed in humans.

Learning and memory—Newborn hippocampal neurons have been implicated in many roles associated with memory and learning (Terranova et al., 2019; Zhao et al., 2008), such as the discrimination of temporal contexts (Rangel et al., 2014), cognitive flexibility (Anacker and Hen, 2017; Garthe et al., 2016), and even forgetting (Frankland et al., 2013). Animal studies show that impairments in AHN can result in specific cognitive deficits, for example in spatial relational memory acquisition (Dupret et al., 2008), the retention of long-term spatial memories (Deng et al., 2009) and in contextual fear conditioning (Saxe et al., 2006; Zhang et al., 2021). Conversely, positive regulators of AHN (such as environmental enrichment, astaxanthin supplementation, administration of ginseng, etc.) are all linked to improvements in learning and memory performance in animals, further implicating the role of newborn neurons in these cognitive processes (Sakalem et al., 2017; Yau et al., 2015; Yook et al., 2016). A recent study in which researchers genetically increased NSC cycle activity and numbers by symmetric proliferative divisions in mice found that the resulting increase in neurogenesis compensated the age-dependent decrease in it, rescuing allocentric navigation and contextual memory, hence rejuvenating critical aspects of brain function (Berdugo-Vega et al., 2020). In humans, bilateral surgical lesions of the hippocampal formation result in memory deficits (Scoville and Milner, 1957). While studies relating hippocampal neurogenesis with memory performance in humans are sparse for obvious reasons, one study in patients with chronic drug-resistant temporal lobe epilepsy found that the proliferation and neuronal differentiation capacity of adult human NSCs *in vitro* (which the authors claim is closely linked to neurogenic potential *in vivo*) was correlated with each patient's ability to store and recall memories prior to surgery (Coras et al., 2010). They showed that patients with high proliferation capacity stem cells had a normal memory performance prior to epilepsy surgery, while patients with low proliferation capacity stem cells showed severe learning and memory impairment, which suggests that the encoding of new memories is related to the regenerative (neurogenic) capacity of the hippocampus. Abilities such as encoding new memories of episodes or facts, working memory and processing speed exhibit an age-associated decline in both cross-sectional and longitudinal studies. And cognitive stimulation might protect against these declines by enhancing neurogenesis (Hedden and Gabrieli, 2004).

1.3. Neural stem cells

NSCs are the source of new neurons in the adult mammalian brain and may be a promising therapeutic target. Specifically, targeting neurogenesis through pharmacological or non-pharmacological means may be beneficial for the treatment of a wide array of disorders, ranging from MDD and anxiety disorders to neurodegenerative diseases such as AD and PD (Berger et al., 2020; Coras et al., 2010). However, enhancing the levels of neurogenesis may not always be beneficial, as witnessed by some pathological conditions including epilepsy, where seizures induce neurogenesis and where decreasing its levels may be beneficial (Scharfman and Hen, 2007). Animal models of temporal lobe epilepsy show that prolonged seizures result in an increase of newborn neurons in the DG, but that some of them fail to migrate, differentiate and integrate properly (Scharfman, 2004). This type of aberrant neurogenesis might contribute to recurrent seizures in animals, and a similar process might be at play in some patients with mesial temporal lobe epilepsy (Parent et al., 2006). Since the neurodegenerative diseases we focus on in this review are associated with a reduction,

rather than an increase in neurogenesis (Winner and Winkler, 2015), we will describe NSCs and the regulation of their proliferation in the adult mammalian brain in this section. The potential pitfalls of aberrant neurogenesis and/or its increase to supraphysiological levels will be discussed in more detail in the conclusion of this review.

Types of stem cells—Stem cells (and by proxy NSCs) are defined on the basis of two functional properties: a seemingly unlimited capacity for self-renewal and multipotency (Seaberg and van der Kooy, 2003). Self-renewal refers to the ability of these cells to undergo division, maintaining their ability to differentiate into multiple mature cell types - neurons, astrocytes, and oligodendrocytes in the case of NSCs. There are three types of stem cells with the potential to be used in stem cell-based therapies. Two of these are physiological, present at different stages of life: multipotent adult stem cells (ASCs) and pluripotent embryonic stem cells (ESCs), while one type is artificially engineered from a non-pluripotent cell; induced pluripotent stem cells (iPSCs) (Alvarez et al., 2012; Herreros-Villanueva, 2014; Mousavinejad et al., 2016). Although adult NSCs are multipotent, they generate specific cell types depending on the neurogenic region they belong to, resulting in a different outcome of neurogenesis in those areas. SVZ NSCs become fate restricted during embryonic development and produce oligodendrocytes and interneurons of the OB, which are inhibitory in nature (Ghosh, 2019). In contrast, the NSCs in the SGZ generate only excitatory granule neurons of the DG, and normally do not produce oligodendrocytes – their multipotency *in vivo* is restricted by the RNase III protein Drosha (Rolando et al., 2016). Other notable differences are described elsewhere (Ghosh, 2019; Nakafuku and Águila, 2019; Urbán and Guillemot, 2014) and include the involvement of migratory maturation in SVZ neurogenesis, while SGZ newborn neurons do not require much migration and are restricted to the granule cell layer of the DG.

In the hippocampus, the process of neurogenesis starts with quiescent NSCs. These cells are also called radial glia-like (RGL) cells and they consist of several subpopulations with different properties. In a recent study they were divided into two classes on the basis of their morphology: type α cells and type β cells (Gebara et al., 2016). Type α cells can give rise to neurons, astrocytes and type β cells, while type β cells do not proliferate and may represent an intermediate state in the transformation of type α cells into astrocytes. Once these quiescent cells are activated, they can divide symmetrically to generate additional RGLs (self-renewal), or asymmetrically to produce proliferating intermediate progenitor cells (IPCs, or Type-2 cells). IPCs are lineage-restricted and undergo limited rounds of rapid cell division, giving rise to bipolar neuroblasts (Type 3 cells) and then immature neurons (Berg et al., 2018; Bonaguidi et al., 2012). A study carried out in rats showed that half of these newborn neurons die before they are able to mature and become integrated granule neurons of the DG (Dayer et al., 2003).

Regulation of proliferation—Studies in rodents have shown that the number of NSCs decreases with age, which contributes to reduced neurogenesis (Kuhn et al., 1996; Maslov, 2004). Neurogenesis in rodents also decreases with age as a consequence of several other factors, including decreased proliferation and growth factor signaling (Shetty et al., 2005; Tropepe et al., 1997), increased levels of corticosteroids (Drapeau and Nora Abrous,

2008; Montaron et al., 2006), stem cell senescence (Audesse and Webb, 2020; Cutler and Kokovay, 2020) and epigenetic drift (Chen and Kerr, 2019). However, how aging affects the specific dynamics of processes such as NSC differentiation is not clear. While NSCs are a heterogenous populations, with subsets that may be unevenly affected by aging (Kuhn et al., 2018), they seem to shift from self-renewal during early development towards differentiation via asymmetrical division with aging (Nicaise et al., 2020). Glucocorticoid oscillations have been identified as one of the regulators of NSC proliferation during aging *in vivo*, possibly through an epigenetic mechanism, but it is not yet known how they affect differentiation (Schouten et al., 2020).

Stem cell frequency and self-renewal potential, as well as overall proliferation rate all decline with age in the mouse forebrain (Molofsky et al., 2006) and hippocampus (Lee et al., 2012). Curiously, despite this age-dependent loss of NSCs and a reduction in neurogenesis, when NSCs are removed from the aged environment (expanded *in vitro*), they retain their ability for proliferation and multilineage differentiation, generating functional neurons that are similar to that of NSCs in adult mice, albeit with lower efficacy (Ahlenius et al., 2009). This suggests that, with aging, neurogenic niches become unfavorable for neurogenesis. While some authors emphasize that this behavior is dissimilar to other stem cells and identify cell-extrinsic factors in the aged brain as the most relevant aspect that makes NSCs susceptible to aging (Schultz and Sinclair, 2016), it should be noted that age-dependent, intrinsic changes in the NSCs themselves seem to play a role as well (Ahlenius et al., 2009). Intrinsic and extrinsic factors that regulate NSCs have recently been reviewed elsewhere (Matsubara et al., 2021). These intrinsic changes, however, do not seem to affect the potential for functional integration of neurons differentiated from the adult and aged SVZ, in comparison to the neurons differentiated from NSCs of embryonic lateral ganglionic eminence. Taken together, these properties are highly relevant for potential future therapeutic applications, which will be described in more detail in section 4.

2. Neurogenesis in neurodegenerative diseases

Neurodegenerative diseases are a heterogeneous group of brain disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and others (Cheyuo et al., 2019). Despite the different clinical manifestations and pathological mechanisms, progressive neuron loss/death and structural and functional defects in the neural system are common features of these diseases (Chi et al., 2018). Many studies suggest that dysregulated neurogenesis is a pivotal contributor to neurodegenerative diseases. While several other recent reviews focus on neurogenesis in the context of AD (Essa et al., 2022; Farioli-Vecchioli et al., 2022; Liu et al., 2021), our review explores neurogenesis on a broader level and describes how the most common geroscience interventions affect it. In this section, we mainly focus on the changes of neurogenesis in AD and PD, the two most prevalent neurodegenerative diseases, and briefly discuss other neurodegenerative diseases with reported defects in neurogenesis, such as HD, ataxia telangiectasia (A-T), and Cockayne syndrome (CS).

2.1. Alzheimer's disease

AD is a progressive neurologic disorder primarily affecting elderly adults and eventually leading to a severe cognitive decline (Alzheimer's Association, 2019). It is the leading cause of dementia, which is predicted to affect 152.8 million people by 2050, highlighting the substantial social and economic burden worldwide (GBD 2019 Dementia Forecasting Collaborators, 2022). Memory impairment is the typical clinical symptom of AD (Jahn, 2013), and other clinical features involved in disease progression include executive dysfunction, language disorder, vision and olfactory impairment, and changes in mood and behavior (Graff-Radford et al., 2021; Kumar et al., 2018). AD patients are classified into early-onset Alzheimer's disease (EOAD) (< age 65), also known as familial AD and late-onset Alzheimer's disease (LOAD) (> age 65), which is more related to highly prevalent sporadic AD (Babcock et al., 2021). Deleterious mutations in amyloid precursor protein (*APP*), presenilin 1 (*PS1*), and presenilin 2 (*PS2*) are risk factors for EOAD. And Apolipoprotein E (*APOE*) is the major susceptibility gene associated with LOAD (Meyer et al., 1998). They will be discussed in more detail in section 3 of this review.

The progression of AD is associated with aging (Hou et al., 2019). Accumulated DNA damage and attenuated repair could exacerbate AD progression in both humans and mice (Hou et al., 2019). Neurons affected in AD exhibit mitochondrial dysfunction, suggesting a critical role of mitochondria in neuronal degeneration (Kerr et al., 2017). Additionally, the level of nicotinamide adenine dinucleotide (NAD^+), a main contributor to mitochondrial dysfunction, decrease with age and in AD (Fang et al., 2017). Inflammation may be another critical neuropathological factor leading to neurodegenerative processes in AD (Fakhoury, 2018; Wang et al., 2019).

AD is more prevalent in females than in males (Alzheimer's Association, 2019). Females also exhibit greater cognitive decline than males (Rodríguez et al., 2008; Sohn et al., 2018). The negative association between hippocampal volume and memory performance is observed exclusively in older women (Zheng et al., 2017). Female mice also exhibit an earlier age-related reduction of neurogenesis than male mice in the 3xAD animal models, as well as mitochondrial dysfunction (Demarest et al., 2020; Rodríguez et al., 2008). This deviation may be explained by the different levels of circulating sex hormones such as estrogen and testosterone (Clinton et al., 2007).

Except for genetic risk factors, aging and sex, some behaviors, such as sleep disturbance and caloric intake, have also been considered as risk factors for AD. Caloric restriction reduces Aβ and improves memory in AD mice (Hornsby et al., 2016; Schafer et al., 2015). Though many risk factors of AD have been revealed, the underlying mechanisms are still largely unknown, which impedes the discovery of drugs and treatment for the disease. Given the high complexity of AD, focusing on a single gene or pathway might be limiting. Treatments targeting aging, DNA repair, inflammation, and mitochondrial homeostasis as a combined strategy are more promising. And neurogenesis is a crucial modulator connecting them all.

2.1.1. Neurogenesis in AD patients—The hippocampus is one of the most affected brain areas in AD patients (Jahn, 2013). As AD progresses, tangles and plaques develop earlier in the hippocampus, entorhinal cortex, and olfactory bulb before being observed

in the cortex (Price et al., 1991). These brain areas involved in neurogenesis might be particularly vulnerable in AD and reflect the disease process. In a genome-wide gene expression association study of AD, neurogenesis-related genes were identified as the top cluster (Talwar et al., 2014). A more recent genetic meta-analysis of LOAD patients also confirmed several novel variants, such as *TREM2*, *ADAM10* and *GPRC5B*, which were related to immunity, lipid processing, tau and APP pathways (Kunkle et al., 2019). These genes also play roles in the regulation of neurogenesis, further confirming the possible relationship between neurogenesis and AD (Kurabayashi et al., 2013; Raha et al., 2017; Zhuang et al., 2015). Additionally, several genes involved in regulating cell survival and growth, such as *CDC42*, *BDNF*, and *VEGFA*, were reduced in AD patients, which may negatively impact neurogenesis (Baptista and Andrade, 2018; Yan et al., 2019). An epigenetic study on AD patients also found that the hypermethylated genes in AD hippocampus were mostly related to neural differentiation and neurogenesis, supporting neurogenesis-related genes as the main targets of epigenetic changes in AD hippocampus (Altuna et al., 2019). Thus, understanding the mechanisms involved in dysregulation of neurogenesis should provide new opportunities for developing preventive and regenerative therapies for AD.

Although reduced adult neurogenesis during healthy aging has been reported (Morgenstern et al., 2008), its direct effects in AD are still elusive. Earlier studies on AD patients reported increased neurogenesis in the hippocampus (Boekhoorn et al., 2006; Briley et al., 2016; Gomez-Nicola et al., 2014; Jin et al., 2004; Mikkonen et al., 1999) and the increase was associated with higher burdens of Alzheimer-type pathology (Perry et al., 2012; Wharton et al., 2005). The upregulated neurogenesis might be a temporal compensatory mechanism to replenish cells lost through degeneration in AD, which will result in the depletion of the neural progenitor cell (NPC) pool. A similar result was found in an *in vitro* study, in which NPCs that were derived from fibroblasts of AD patients exhibited accelerated neural differentiation and reduced progenitor cell renewal (Meyer et al., 2019). In contrast, as mentioned before, Moreno-Jimenez et al. (2019) found that AHN persists throughout life and progressively declines as AD progresses in the patients (Elena P Moreno-Jiménez et al., 2019). Furthermore, Tobin et al. found that patients with mild cognitive impairment exhibited fewer NPCs than normal subjects, demonstrating a correlation between cognitive function and neurogenesis in AD pathology (Tobin et al., 2019). Similarly, an increased number of SOX2^{+} NSCs seems to correlate with normal cognitive capacity in AD (Briley et al., 2016). Indirect evidence associated with neurogenesis, like reduced hippocampal volume and spatial pattern separation impairment in AD patients (Martínez-Pinilla et al., 2016; Parizkova et al., 2020), also show the possibility of declined neurogenesis in AD subjects. Taken together, AHN decreases with the progression of age in AD patients, and this decrease is linked with impaired cognitive function.

2.1.2.   Neurogenesis in AD animal models—Decreased neurogenesis has been reported in aged mice (Berdugo-Vega et al., 2020; Kirschen and Ge, 2019), as well as in transgenic animal models of AD(Demars et al., 2010; Li et al., 2009; Rodríguez et al., 2009; Zhang et al., 2007). Strikingly, human NSC transplantation restored cognition in an AD mouse model, suggesting the possibility of boosting neurogenesis as an intervention

in AD (McGinley et al., 2018). A summary of neurogenesis studies in AD and other neurodegenerative diseases animal models are presented in Table 1.

The activity of neural precursors may be regulated by risk genes involved in AD such as *APP*, *PS1* and *APOE* (Li et al., 2009; Smukler et al., 2011; Yang et al., 2011). Interestingly, these AD-associated gene mutations suppress multiple stages of neurogenesis in AD mice (Hamilton et al., 2010). Similar to the finding in humans, the deficits in neurogenesis are observed before the development of amyloid plaques in an APP/PS1 mouse model, supporting the hypothesis that altered neurogenesis might be a potential marker for early development of AD (Unger et al., 2016). Studies in the 5xFAD mouse model showed reduced newborn cells in the SGZ (Moon et al., 2014), while NSC proliferation was not impacted (Zaletel et al., 2018), suggesting that the disruption of neurogenesis occurs during differentiation. Interestingly, Choi et al. found that increasing AHN alone did not improve cognition in the 5xFAD mouse model, whereas increasing both AHN and brain-derived neurotropic factor (BDNF) could simulate exercise-induced improvement in learning and memory, highlighting the importance of the health of the local brain environment (Choi et al., 2018). A recent study on humans also showed the protective role of BDNF on hippocampal connectivity in AD pathology (Franzmeier et al., 2021). Given the brain functions not only rely on the existence of neurons, but also on how effectively the large-scale functional networks are engaged in neuronal activities, it makes sense that a healthier neurogenic niche may better repair the damaged neural network and cognitive function. In both 2xTg AD and 3xTg AD mouse models, differentially methylated genes associated with cognitive improvement in the hippocampus were related to neurogenesis and synaptic function, showing that epigenetic changes targeting in neurogenesis might be related to the functions of learning and memory in AD (Lee et al., 2018; Sandoval-Hernandez et al., 2016). For example, the histone deacetylase inhibitor, valproic acid (VPA), which has been suggested as a potential treatment for AD (Bottero et al., 2021), induced the differentiation of adult hippocampal neural progenitors *in vitro* (Hsieh et al., 2004). While still an open question, some have argued that strategies aimed at restoring and/or boosting AHN in both normal elderly people and subjects at high risk of AD could emerge as effective strategies to prevent the onset and/or counteracting the progression of the disease (Li Puma et al., 2021).

2.1.3.   The effects of DNA damage on neurogenesis in AD—Both degeneration and neurogenesis in AD are tightly connected with DNA damage responses and oxidative stress (Barazzuol et al., 2017; Hou et al., 2018; Shull et al., 2009) (Barazzuol et al., 2017; Hou et al., 2018; J. Li et al., 2020; Shull et al., 2009). Increased DNA damage inhibits neurogenesis and promote cell death both *in vivo* and *in vitro*. DNA damage, detected by γH2AX, a marker of DNA double-strand breaks (DSB), accumulates in the brains of AD patients (Lin et al., 2020). Persistent DNA damage by irradiation could compromise hippocampal neurogenesis (Schmal et al., 2019). Reactive oxygen species (ROS) promotes DNA damage and cell death, which contribute to the pathogenesis of AD (Taupin, 2010). Some proteins involved in DNA repair also play a crucial role in neurogenesis. For example, neurons in vulnerable regions of the AD brain, like the hippocampus and frontal cortex, displayed reduced expression of ataxia telangiectasia mutated (ATM) protein and decreased ATM signaling in both humans and mice, which drove abnormal neuronal cell cycle reentry,

ultimately causing cell loss (Shen et al., 2016). Also, loss of NEIL1 or NEIL3, the primary DNA glycosylases for base excision repair (BER), leads to the reduction of proliferation capacity of hippocampal NPCs and impaired learning and memory in mice, likely due to the failure in the removal of hydantoin lesions of single-stranded DNA in NPCs (Regnell et al., 2012; Yang et al., 2019). Mitochondrial DNA damage accumulated in the NSC population with knockdown the DNA repair protein, 8-oxoguanine DNA glycosylase (OGG1), and it shifted the differentiation of NSCs toward to astrocytic lineage (Wang et al., 2011). Lower hippocampal volume and a decline in adult neurogenesis were observed in a mouse model with defective DNA repair due to Polβ haploinsufficiency (Hou et al., 2018; Sykora et al., 2015). In conclusion, neurogenesis is particularly susceptible to DNA damage, which further increases the risk of neurodegeneration in AD progression. Boosting DNA repair may be a promising treatment strategy for AD. Potential DNA repair intervention like NAD$^+$-boosting molecules and its effects on neurogenesis will be discussed in section 4.2.1.

2.2. Parkinson's disease

Parkinson's disease (PD) is the second leading neurodegenerative disease affecting 1–2% of the population age 65 or older, targeting twice as many men as women (Goldman and Fahn, 2020). PD is characterized by neuronal loss in the substantia nigra, which then causes striatal dopamine deficiency and intracellular inclusions, known as Lewy bodies (LBs) (Gibb and Lees, 1988). PD has both motor and non-motor dysfunctions. The motor symptoms are characterized as movement difficulty (slowness and change in gait), muscular rigidity (stiffness), postural instability and tremors in limbs and face (Church, 2021). Nonmotor signs include sleep disturbance, olfactory dysfunction, visual dysfunction, psychiatric symptoms, and cognitive impairment (Obeso et al., 2017).

PD is a heterogeneous and complex disease with multiple genetic, epigenetic, and environmental risk factors. Aging is the leading risk factor (Levi and Michaelson, 2007). Many genes (*SNCA*, *LRRK2*, *VPS35*, *PRKN*, *PINK1*, *DJ-1*, *FBXO7*, and *DNAJC6*) are associated with PD pathology (Goldman and Fahn, 2020). Its pathophysiology is related to aggregated α-Synuclein oligomers, defective mitophagy, increased oxidative stress, calcium imbalance, compromised axonal transport, and increased neuroinflammation (Poewe et al., 2017; Grünewald et al, 2019). Currently, there are no effective treatments for PD except for providing relief of symptoms and slowing down the disease progression (Raza and Anjum, 2019). The initial PD managements, which increased the dopamine levels, like deep brain stimulation and dopamine receptor agonist treatments, also increased both adult SVZ and SGZ neurogenesis in humans and animal models of PD, which might further facilitate learning and memory and coping with mood disorders in PD (Chiu et al., 2015; O'Sullivan et al., 2011; Vedam-Mai et al., 2014). Also, the non-motor symptoms in PD may partly related to impaired olfactory and hippocampal function, raising the potential to slow down the neurodegenerative progression in PD through inducing neurogenesis in these areas (Le Grand et al., 2015; Marxreiter et al., 2013).

2.2.1. Neurogenesis in PD patients—PD patients exhibit hippocampal and olfactory dysfunction (Braak et al., 2003; Regensburger et al., 2014). The hippocampal LB density is correlated with the degree of dementia in PD patients, suggesting that alternations of

hippocampal connectivity could contribute to the emergence of memory deficits (Carlesimo et al., 2012; Churchyard and Lees, 1997). Memory-related hippocampal atrophy and olfactory defects are exhibited in PD patients (Bohnen et al., 2010; Brück et al., 2004). Dopaminergic neural fibers from substantia nigra and ventral tegmental area could innervate the prefrontal cortex and limbic system including hippocampus, suggesting a functional and an anatomical link between nigrostriatal dopaminergic neurons and hippocampal dependent functions (Deniau et al., 1994; Kahn and Shohamy, 2013). In addition, dopaminergic signaling promoted the proliferation and the survival of newborn cells in hippocampus (Winner et al., 2009). Thus, the decreased neural precursors observed in the OB and DG of PD adults may be associated with impaired dopaminergic innervation in these regions (Höglinger et al., 2004). A reduction in the number of Musashi1-positive cells in the SVZ was observed in PD cases, and the expression of Musashi1 proteins had an inverse relationship with the disease duration (O'Sullivan et al., 2011; Ziabreva et al., 2007). Similarly, SOX2-positive cells declined in the hippocampus of PD patients (Winner et al., 2012). Non-motor symptoms, like olfactory dysfunction, depression, and impaired spatial memory are frequently observed in individuals with PD and often occur before the onset of motor symptoms (Berendse et al., 2001; Lim et al., 2018; Pillon et al., 1997). Importantly, a decline of adult neurogenesis in olfactory structures was noted in the early stages of PD (stage 1) (Braak et al., 2003), which corresponded to the olfactory dysfunction observed in PD patients (Regensburger et al., 2014). A recent study on anosmia (loss of smell) in COVID-19 patients also revealed that SARS CoV-2 infection is a risk factor for PD, and that a potential cause of smelling loss could be the impairment of neurogenesis in the olfactory system (Rethinavel et al., 2021). Overall, these findings strengthen the hypothesis that impairments in neurogenesis may contribute to the non-motor pathogenesis of PD.

2.2.2. Neurogenesis in PD animal models—Genes involved in PD (like *SNCA*, *PINK1*, *LRRK2*, *VPS35*…) play important roles in the generation and maintenance of the NSC pool as well as the differentiation and survival of NPCs (Le Grand et al., 2015; Lee et al., 2013; Winner et al., 2011, 2008). Interestingly, the deregulated neurogenesis observed in PD animal models appears to regulate various functions related to non-motor symptoms (including hyposmia, depression and anxiety…) observed in PD, strongly suggesting there is a link between neurogenesis deficits and the progression of PD (Bang et al., 2021; Le Grand et al., 2015). Reduced adult neurogenesis has been reported in different PD animal models. For instance, overexpression of α-synuclein (*SNCA*) compromised neurogenesis in both hippocampus and OB among rats (Kohl et al., 2016), *C. elegans* (Lakso et al., 2003) and mice (Winner et al., 2004). Another study also found a lower adult neurogenesis and abnormal dendrites of the newborn neurons in SGZ and SVZ areas of an LRRK2-G2019S transgenic mouse model, and the reduction could be partially reversed by enhanced physical activity (Winner et al., 2011). Similar observations were obtained from the neurotoxin-induced PD mouse models, with a significantly declined number of newborn neurons in the rodents' hippocampus (Singh et al., 2017; Sung, 2015). Regarding cognitive dysfunctions observed in PD animal models, it is often coupled with reduced hippocampal neurogenesis. For example, mice lacking *Dorfin*, a RING finger E3 ubiquitin ligase implicated in PD, showed reduced AHN and impaired contextual fear conditioning, which is highly hippocampal-dependent (Park et al., 2015). Similarly, impairment of hippocampal

neurogenesis-dependent pattern separation was observed after overexpression of a-synuclein in rats, which could be rescued by voluntary running, implicating activating AHN may serve as a neuroprotective treatment to non-motor symptoms in PD (Crowley et al., 2018). There is a strong correlation between dopaminergic degeneration and Parkinsonism (Bernheimer et al., 1973). A promising study to reprogram astrocytes to functional neurons found a therapeutic effect on dopamine levels and motor phenotypes in a PD mouse model (Qian et al., 2020). Dopamine promotes the proliferation and survival of newborn cells in the embryo and adulthood of rodents (Ohtani et al., 2003; Takamura et al., 2014). Depleting dopamine inhibited NPC generation in PD mice (Höglinger et al., 2004). These observations suggested that impaired neurogenesis in PD might be a consequence of dopaminergic denervation. In conclusion, hippocampal neurogenesis associated dysfunctions are common in PD, and likely contribute to cognitive impairment and emotional disorders, which can be relieved by increasing AHN conversely. The profound alterations of neurogenesis in PD have raised attention and may provide a novel strategy for effective therapeutics for it.

2.3. Other neurodegenerative diseases

Next, we will briefly introduce other neurodegenerative diseases, including HD, Ataxia telangiectasia (A-T) and Cockayne syndrome (CS). HD is known as a progressive neurodegenerative brain disease (Ruzo et al., 2018). A-T and CS are the premature aging diseases, and studies of these diseases will contribute to our knowledge of DNA metabolism, cellular senescence, and stem-cell differentiation during aging (Dyer and Sinclair, 1998).

2.3.1.   Huntington's disease—HD is an autosomal dominant neurodegenerative disorder caused by an expansion of the polyglutamine (poly Q) tract in the Huntingtin (HTT) protein (Ruzo et al., 2018). The polyQ repeat length is associated with disease severity, e.g., a person with more than 36 repeats is more likely to develop HD (Rego and de Almeida, 2005). Neuronal loss in the striatum, cortex, and hippocampus, which results in cognitive dysfunction and severe motor impairments, is one typical feature of HD (Ruzo et al., 2018).

The neurons differentiated from iPSCs of HD patients exhibited alterations of growth, metabolism, survival, and death (Lim et al., 2017). In light of this, the mutant *HTT* gene has been reported to induce the cell cycle re-entry of neurons and impaired neuronal differentiation and further reduce the survival of newborn neurons in rodent striatum and hippocampus (Manickam et al., 2020). In addition, deficits in AHN have been reported in the R6/2 (Gil et al., 2005), the R6/1 (Lazic et al., 2006), and the YAC128 transgenic mouse model (Simpson et al., 2011) of HD, which might underlie the cognitive deficits associated with HD (Gil-Mohapel et al., 2011).

To date, there is no cure for HD, and the treatments available are limited to symptomatic clinical management (Tabrizi et al., 2019). Therapies using stem cell technology have been proposed as a promising treatment of HD (Bachoud-Lévi et al., 2021). Cell therapies aiming to enhance endogenous neurogenesis have shown promising results in HD animal models (Lee et al., 2009; Pollock et al., 2016; Snyder et al., 2010). It was also shown that a combination of stem cell and gene therapy could improve motor functions and extend the lifespan of HD mice (Cho et al., 2019). A recent review also summarizes the preclinical

studies using stem cells in HD animal models, highlighting the benefits and promises of stem cells used as a promisor therapeutic strategy for HD (Colpo et al., 2019). Thus, neurogenesis-based cell treatments still offer hope for the future therapies of HD.

2.3.2.   Ataxia telangiectasia—A-T is a rare and complex genetic neurodegenerative disorder (affecting ∼ 1/40 000–1/100 000 people), caused by mutations in the *ATM* gene (Taylor et al., 2015). ATM is a sensor of DSBs that is involved in cell cycle checkpoints (Savitsky et al., 1995), and oxidative stress response (Liu et al., 2005). Both A-T patients and ATM-deficient mice exhibit enhanced oxidative damage (Reichenbach et al., 2002; Stern et al., 2002).

ATM is essential in early brain development and adult neurogenesis (Allen et al., 2001; Enriquez-Rios et al., 2017). It is critical for cell proliferation, DNA repair, and apoptosis after DNA damage in both non-cycling and proliferative cells in mice (Enriquez-Rios et al., 2017). Lacking ATM was found to provide resistance to irradiation induced apoptosis and proliferation arrest in mice SVZ, indicating that a failure to activate DNA damage responses disturbs the homeostasis of NSC between quiescence and activation (Barazzuol et al., 2017). NSCs in the hippocampus of ATM$^{-/-}$ mice displayed an abnormally high rate of proliferation and decreased cell survival *in vivo*, and a weakened ability to differentiate to neurons and oligodendrocyte *in vitro* (Allen et al., 2001). However, other researchers noted that ATM deficiency did not impair cell proliferation and differentiation, using an immortalized human neural stem cell line (ihNSC) (Carlessi et al., 2009). Conversely, ATM depletion could attenuate the short-term apoptotic response to irradiation-induced DNA damage (Carlessi et al., 2013). Possible explanations of these inconsistent results are that i) the NSCs obtained from different brain regions may have distinct characteristics and developmental patterns; ii) ATM may impact brain functions through distinct mechanisms in different brain regions and diverse cell populations. Indeed, a reduced yield of GABAergic neurons in the ATM-deficient ihNSCs was found, implicating that ATM may not be required for overall neurogenesis, but specific to a GABAergic neuronal differentiation (Carlessi et al., 2013). Notably, GABA signaling regulated NSC proliferation and growth through the ATM/ATR-related phosphorylation of γ-H2AX in mouse ES and NCS cells (Andäng et al., 2008), which is consistent with human clinical findings. Specifically, a lower GABA level has been found in the cerebellum of an A-T patient when compared with control (Perry et al., 1984), and a GABA analog could ameliorate the ataxia manifestation (Gazulla and Benavente, 2006).

2.3.3.   Cockayne syndrome—Cockayne syndrome (CS) is a progressive developmental and neurodegenerative disorder resulting in premature death in childhood (Karikkineth et al., 2017). CS patients show severe photosensitivity, growth retardation, accelerated aging, DNA repair and transcription defects, and CNS abnormalities (Ciaffardini et al., 2014). Mutations in CSA (*ERCC8*) and CSB (*ERCC6*) cause CS (Laugel et al., 2010; Okur et al., 2020). About 80% of CS cases are caused by mutations in CSB (Vessoni et al., 2016). The CSB protein is essential in various DNA repair processes, including BER, nucleotide excision repair (NER) and double-strand break repair (DSBR) (Tiwari et al., 2021).

Neuronal differentiation and neurogenesis are compromised in human CSB-deficient NSCs and iPSCs (Ciaffardini et al., 2014; Vessoni et al., 2016). Likewise, genes related to neurogenesis were also down-regulated in the fibroblasts of CS patients (Wang et al., 2014). In contrast, this process was not affected in the CSB-deficient mouse model (Sacco et al., 2013). CSA and CSB proteins possess an essential role in the turnover of p53 transcription factors by promoting their ubiquitination and degradation (Latini et al., 2011). Altered p53 activity disrupts the proliferation and differentiation of NPCs in adult neurogenesis (Armesilla-Díaz et al., 2009; Medrano and Scrable, 2005). Accordingly, dysfunction of CSA and CSB may result in defective neurogenesis, further contributing to the dramatic and complex phenotypes in CS patients.

3. The role of the key aggregation-prone proteins in neurogenesis

Two hallmarks of AD brains are the aggregation of Aβ in extracellular plaques and intraneuronal neurofibrillary tangles formation by hyperphosphorylated tau proteins (Alzheimer's Association, 2019). *APP*, *PS1*, *PS2* and *APOE* are identified as the high-penetrant genetic factors contributing to AD (Van Cauwenberghe et al., 2016). The aggregation of α-synuclein in LBs and Lewy neurites is a characteristic feature of PD pathology (Xu and Pu, 2016). Nuclear accumulation, misfolding and abnormal aggregation of the mutant HTT results in selective neuronal neuronal loss predominantly in the striatum and the cortex (McColgan and Tabrizi, 2018). In this section, we will discuss the relationships of those key aggregation-prone proteins with neurogenesis, and an overview on the roles of these proteins in AHN is illustrated in Figure 1.

3.1. Tau

Tau protein is involved in microtubule assembly and stabilization, and commonly found in the cytosol and axons of neurons (Barbier et al., 2019). Hyperphosphorylated tau proteins, which lead to neuritic plaques and neurofibrillary tangles, represent one of the hallmarks of AD (Alzheimer's Association, 2019). Prominent clinical heterogeneity in the hyperphosphorylated species of soluble, oligomeric, seed-competent tau was found in AD patients, implying that targeting tau is a potential personalized therapeutic approach to slow AD progression (Dujardin et al., 2020).

The relationship between tau and adult neurogenesis has been reviewed elsewhere (Fuster-Matanzo et al., 2012; Houben et al., 2021; Pristera et al., 2013). Tau is able to induce AHN-related deficits, including suppression of proliferation, neuronal atrophy and malfunction, impaired learning and memory, and downregulated GABA signaling, in an age-dependent manner (Dioli et al., 2017). Depletion of tau enhanced neurogenesis and rescued the stress-induced reduction of proliferation in both DG and SVZ of mice (Criado-Marrero et al., 2020a; Dioli et al., 2021, 2017). A recent study revealed that tau impaired AHN by suppressing GABAergic transmission in the hippocampus (Zheng et al., 2020). Strengthening the GABAergic transmission in 3xTg AD mice could efficiently rescue AHN deficits caused by tau accumulation and improve AHN-dependent cognitive functions (Zheng et al., 2020). Tau participates in a variety of cellular cascades regulating cell survival and proliferation. For example, the glycogen synthase kinase-3β (GSK-3β), a

crucial tau kinase that plays a role in its hyperphosphorylation, was suggested to be related to the cause of AD and could modulate adult neurogenesis (Liu et al., 2021). The p21-activated kinase 3 (Pak3), regulating synaptic plasticity and neurogenesis, was significantly reduced in the hippocampus and frontal cortex of postmortem brains from AD patients (Fuchsova et al., 2016), but was increased in mice when the tau gene *MAPT* was deleted (Criado-Marrero et al., 2020a). Activation of the Wnt/β-catenin signaling pathway could also restore neurogenesis reduced by the aggregate tau mutant (Joseph et al., 2017). Finally, neurogenesis requires dynamic control over the cytoskeleton and microtubules, and tau proteins facilitate this process (Morris et al., 2011). Together, targeting tau related pathways (like GSK-3β-PI3K signaling and Wnt/β-catenin signaling) to increase neurogenesis might be a valuable approach against AD. However, the potential molecular mechanisms underlying the relationship between tau and adult neurogenesis still need to be further explored.

3.2.   Aβ and APP

Aβ peptides are 36–43 amino acids derived from APP by proteolytic cleavage (Tarasoff-Conway et al., 2015). Aβ accumulation and toxicity can cause neuronal loss and trigger AD pathology (Tillement et al., 2011). Elevated concentrations of Aβ42 and tau in cerebrospinal fluid are biomarkers of AD diagnosis (Fagan and Perrin, 2012), and Aβ42/Aβ40 ratio could further help the separation of AD dementia from other dementia disorders (Hansson et al., 2019). Anti-Aβ drugs had been developed, but many failed in clinical trials, leading to heated debates on the plausibility of the amyloid hypothesis. Recently, FDA approved the first drug, Aduhelm (aducanumab), targeting Aβ plaques removal, but has not been fully clinically demonstrated to be effective for cognition improvement (Mahase, 2021). It is reported that Aβ plaques begin accumulating before AD symptom appears, as early as in 20s (Gonneaud et al., 2017). Cleaning amyloid in AD patients who already have dementia would be too late since the brain has already been severely damaged. Therefore, discovering appropriate early clinical biomarkers of AD should be a future effort to help prevent AD.

APP proteins have a complex relationship with neurogenesis. The soluble APPα (sAPPα) cleaved by α-secretase is neuroprotective, showing the capability to induce NPC proliferation (Chen and Tang, 2006). In contrast, Aβ deposits cleaved by β-secretase or γ-secretase are more toxic to neurogenesis. Depletion of Aβ peptide reduced tau inclusions and induced AHN in the rat hippocampus (Morrone et al., 2020). Furthermore, reducing the accumulation of Aβ plaques after disease progression was accompanied by increased adult neurogenesis in a 2xAD mouse model (Calió et al., 2021). Interestingly, researchers found that the formation and accumulation of intracellular Aβ oligomers could affect the OB neurogenesis in Tg2576 transgenic mice prior to the neurodegenerative progress(Scopa et al., 2020). It is further suggested that impaired neurogenesis is an early marker of AD progression (Price et al., 1991; Unger et al., 2016), emphasizing that targeting the early stages of neurogenesis deficits could be an excellent approach against AD. Combination of drugs targeting Aβ deposits clearance and neurogenesis replenishing may be a promising treatment in AD therapy.

3.3. PS1 and PS2

Presenilins are essential components of the γ-secretase complex, which cleave APP to soluble Aβ peptides (De Strooper et al., 1998). A diminished neural progenitor population was reported in the PS1$^{-/-}$ mouse brain (Yang et al., 2000), resulting in a perinatal lethality (Donoviel et al., 1999; Shen et al., 1997). PS1 mutations produced premature neurogenesis and reduced the number of newborn neurons from iPSCs derived from familial AD patients (Arber et al., 2021). Furthermore, downregulation of PS1 in hippocampal NPCs leads to progressive cognition deficits (Bonds et al., 2015). On the contrary, lacking PS1 or PS2 did not influence cell-intrinsic AHN in mice (Dhaliwal et al., 2018). However, some studies confirmed the critical role of PS1 in neurogenesis related to differentiation and dendritic morphogenesis of NPCs (Hernandez-Sapiens et al., 2022). Thus, presenilins have different roles regarding embryonic development and adult neurogenesis. The premature and abnormal features of newborn neurons mediated by presenilins might contribute to neurodegeneration in AD.

3.4. APOE

Humans have three major *APOE* alleles: *ε2*, *ε3*, and *ε4* (van der Lee et al., 2018). *APOE ε4* is associated with an increased risk of AD, and approximately 40% of LOAD patients carry this allele (Corder et al., 1993; Liu et al., 2013). *APOE ε4* carriers showed high levels of Aβ deposition in the brains of elderly and AD subjects (Serrano-Pozo et al., 2021). *APOE* variants have also been reported to contribute to the pathogenesis of dementia in PD patients (Brockmann et al., 2017).

APOE is necessary to maintain the DG neural progenitor pool (Yang et al., 2011). Lack of it may temporarily increase the proliferation of early NPCs in the DG, but eventually lead to the depletion of type I NPC pool over time *in vitro* (Yang et al., 2011). Similarly, lower NPCs and fewer dendritic branches were observed in the hippocampus of APOE KO mice, while cell survival and differentiation were intact (Tensaouti et al., 2018). In addition, an increase in AHN was observed in young adult female APOE2 mice, aged female APOE KO mice, and aged female APOE3 mice compared with control mice (Koutseff et al., 2014; Rijpma et al., 2013). In contrast, both sexes of young adult APOE4 mice and aged female APOE4 mice displayed reduced neurogenesis, highlighting the age- and sex-dependent APOE polymorphisms in adult neurogenesis (Koutseff et al., 2014; Rijpma et al., 2013). APOE4 transgenic mice also exhibited impaired working memory and abnormal neuronal development in the DG (Hartman et al., 2001; Li et al., 2009; Tensaouti et al., 2020). Interestingly, the decreased survival of GABAergic interneurons in APOE4 mice was accompanied by diminished presynaptic GABAergic input-mediated maturation of newborn neurons and elevated tau phosphorylation, suggesting the causable regulation of APOE in neurogenesis (Li et al., 2009). In summary, these data may help to explain the emergence of cognitive decline in humans carrying the *APOE ε4* allele and provide a link between the *APOE ε4* allele and neurodegenerative diseases.

Whether inducing neurogenesis can ameliorate the deteriorations caused by APOE is still uncertain. Few studies have addressed this question. It seems that some physical manipulations inducing neurogenesis, like environment enrichment (EE) and brain injury,

didn't work on APOE4 mice (Hong et al., 2016; Levi and Michaelson, 2007). Conversely, physical exercise could improve hippocampal-dependent cognition and increased the levels of BDNF and tyrosine kinase B (TrkB) in the APOE4 mice (Nichol et al., 2009). However, the researchers haven't checked the status of AHN in these mice, which makes it difficult to confirm whether it is caused by enhancement of neurogenesis or not (Nichol et al., 2009). Further studies are needed to explore the effects of other interventions which could increase AHN (e.g., caloric restriction or pharmacological approaches) on APOE4 dysfunction.

3.5. α-synuclein

SNCA/PARK1, the gene that encodes α-synuclein, was the first gene identified to be associated with PD (Polymeropoulos et al., 1997). Evidence showed that α-synuclein regulates the production of dopamine (Yu et al., 2004). It also interacts with tau and drives the formation of pathological inclusions both *in vivo* and *in vitro* (Badiola et al., 2011; Giasson et al., 2003; Uemura et al., 2020). A decline of AHN is exhibited in an α-synuclein overexpression rat model (Kohl et al., 2016) and after intranasal administration of α-synuclein in mice (Sherstnev et al., 2021). Moreover, mutant α-synuclein aggravated age-related reduction of neurogenesis in the mouse SVZ and OB (Winner et al., 2008). Conversely, depleting α-synuclein resulted in enhanced neurogenesis in mice DG (Winner et al., 2012). In conclusion, α–synuclein aggregates interfere with the proper regulation of AHN, which mediates PD pathology, highlighting the necessity to further investigate whether stimulation of neurogenesis could mitigate the symptoms caused by α-synuclein in PD patients.

4. Interventions to increase neurogenesis

Here, we group the neurogenesis interventions into distinct categories: (1) non-specific physical/metabolic manipulations, (2) pharmacological approaches and, lastly, (3) genetic and reprogramming strategies. Special emphasis will be given to aging-related interventions and compounds that influence known metabolic pathways in aging, such as AMPK, mTOR and sirtuins. Genetic strategies will be skipped due to space constraints and because they have been only used in animal models so far. Cellular reprogramming approaches have been reviewed elsewhere recently (Rando and Jones, 2021). The summary of how the manipulations affect neurogenesis are shown in Figure 2.

4.1. Non-specific physical/metabolic manipulations

There are several non-specific physical/metabolic positive regulators of neurogenesis, such as physical exercise (PE), environmental enrichment (EE) and caloric restriction (CR). Interestingly, most of these manipulations have also been associated with increased lifespan and/or healthspan in model organisms. For example, some studies have shown that EE either increases lifespan in mice (Arranz et al., 2010; Thanos et al., 2016; Yamashita et al., 2018) or results in a trend of mean lifespan extension (McMurphy et al., 2018). The effects of EE on healthspan have been reviewed elsewhere (Queen et al., 2020), and the intervention, if translatable, holds promise for extending human healthspan. PE induces similar effects on healthspan in mice (Garcia-Valles et al., 2013), but the effects on lifespan extension have not been clearly established. Some studies showed lifespan extension in rats (Ji et al.,

2018), no effect on lifespan in mice (Garcia-Valles et al., 2013) or even reduced lifespan in female rats (Karvinen et al., 2015). While further research is needed to establish a causal relationship between PE and lifespan, current observations point to a beneficial effect on humans, reducing the mortality risk (Lee et al., 2014) and improving multiple health indices (Pasanen et al., 2017), recently summarized elsewhere (Carapeto and Aguayo-Mazzucato, 2021). Lastly, CR is the most robust intervention to increase lifespan and healthspan in species ranging from the budding yeast (Jiang et al., 2000) to rhesus monkeys (Colman et al., 2014). However, some researchers warn that since it is still not completely clear if these benefits result from slowing the aging process or merely avoiding obesity, further studies are needed to ascertain if CR and related interventions (such as intermittent fasting and ketogenic diets) should be recommended for healthy (non-obese) people (Lee et al., 2021).

Environmental enrichment—EE is a somewhat vague concept, commonly defined as "an animal husbandry principle that seeks to enhance the quality of captive animal care by providing the environmental stimuli necessary for optimal psychological and physiological well-being" (Shepherdson et al., 1998). In the case of rodents, it usually means housing them in larger cages that contain a variety of objects that they can interact with, such as plastic tubing, igloos with saucer type wheels, and other various plastic hutch-like toys (Slater and Cao, 2015).

In mice and rats, exposure to EE has long term positive effects on memory and learning (Hymovitch, 1952; Yau et al., 2015), albeit inconsistently (Singhal et al., 2019a, 2019b), and is associated with significantly more new neurons in the DG (Clemenson et al., 2015a). EE is a robust manipulation that is able to induce an increase in AHN across the lifespan of mice, with minor differences between strains (Kempermann et al., 2002, 1998b, 1998a; Leal-Galicia et al., 2008). Housing female 5xFAD transgenic mice in an EE (toys and a running wheel) reduced the Aβ plaque load and vivified AHN (Ziegler-Waldkirch et al., 2018). Similarly, exposure to EE (with toys and a tilted running wheel) restored AHN in a 3xTg-AD mice (J. Rodriguez et al., 2011). EE may also slow the onset and progression of HD (Mo et al., 2015) and restore the deficits in AHN in R6/1 mice (Lazic et al., 2006). A causal link between AHN and EE has been established in a study that exposed GFAP-TK mice to repeated social defeat (a type of psychosocial stress), followed by exposure with EE. The same study showed that repeated social defeat led to a submissive and depressive-like phenotype that was rescued by subsequent exposure to EE, but only if AHN was not disrupted through valganciclovir administration (Schloesser et al., 2010). However, this study (along with many others) suffers from lack of a precise definition of EE. Namely, the cages were enriched not just with variously sized tubes, but running wheels as well. This is important because physical exercise (usually in the form of voluntary running on the wheel) and cognitive stimulation (in the form of EE in the strict sense) have different effects on the neurogenic process. Specifically, EE exerts a survival-promoting effect on newborn cells, while running induces proliferation of precursor cells (Fabel et al., 2009; Olson et al., 2006). It is thought that voluntary running "primes" the DG by increasing the number of progenitors available for selection, which leads to an increase in AHN only if there is a need for these cells. This could have implications for potential therapeutic effects of EE or voluntary running, as it is possible that some neurodegenerative changes might

be ameliorated by an increase in NSC proliferation (running), and not through an increased survival of newborn neurons (EE) (or vice versa). For a more thorough discussion about the differences between EE and PE, we point the reader to Rogers et al., 2019.

Physical exercise—PE is usually considered as an "activity and training that causes a substantial increase in heart rate that differs significantly from resting heart rate" (Svensson et al., 2015). In animal studies, voluntary running on a running wheel or a treadmill is usually used, like in some models of EE. Despite this similarity, studies show that they should be treated as distinct interventions and that they, in fact, have additive effects (Fabel et al., 2009; Olson et al., 2006).

It has been shown that PE has profound effects on both learning and memory, shown by studies where late exercise (free access to running wheels) after traumatic brain injury reduced working and retention memory impairments in mice (Piao et al., 2013) and where voluntary wheel running was able to counteract cognitive deficits after chronic corticosterone administration in rats (Yau et al., 2012). It is thought that these positive effects of PE are related to increased levels of neurotrophic factors, elevated expression of anti-inflammatory cytokines, and reduced levels of pro-inflammatory cytokines and activated microglia (Svensson et al., 2015). In regard to neurogenesis itself, running was able to increase cell proliferation in the mouse DG (van Praag et al., 1999), restore hippocampal cell proliferation following chronic administration of corticosterone in rats (Yau et al., 2012) and peripheral administration of lipopolysaccharide in mice (Wu et al., 2007). Aged transgenic mice that exercised on a treadmill displayed improved cognitive function, which was associated with suppressed neuronal cell death in the hippocampus (Um et al., 2011). Similar to EE, PE in the form of voluntary running was able to restore hippocampal neurogenesis in a mouse model of AD (J. Rodriguez et al., 2011). Interestingly, despite the fact that both PE and EE are non-specific manipulations with many other effects, their effect on neurogenesis is highly specific, targeting only the hippocampus and not other neurogenic areas of the brain, such as the OB (Brown et al., 2003). While spatially specific, it has been hypothesized that PE influences AHN in a non-specific way: by activating progenitor cell proliferation and thus increasing the potential for neurogenesis, in a time- and dose-dependent fashion (Holmes et al., 2004). Furthermore, newborn neurons induced by prolonged PE seem to integrate rapidly in the aging brain, elevating the complexity of the network and resulting in a rejuvenated hippocampus of mice (Trinchero et al., 2019). Incidentally, plasma transfer from exercised aged mice to sedentary aged mice ameliorated impaired neurogenesis and cognition in the aged hippocampus, showing that the beneficial effects of exercise on the aged brain can be transferred through administration of blood components (Horowitz et al., 2020). This is supported by a recent cellular parabiosis study that used an *in vitro* model of neurogenesis where a human hippocampal progenitor cell line was treated with human serum, showing that reduced physical activity can increase hippocampal cell death and the risk for future cognitive decline and dementia (Du Preez et al., 2021).

Caloric restriction—CR is usually defined as a "reduction of caloric intake - typically by 20 – 40% of *ad libitum* consumption - while maintaining adequate nutrient intake"

(Trepanowski et al., 2011). This term is sometimes used interchangeably with dietary restriction, which is an intervention in which specific macro/micronutrients (e.g., proteins, carbohydrates and amino acids) are restricted, with no reduction in total energy intake (Selman, 2014).

CR overall has positive effects on learning and memory. A study carried out in rats showed that their spatial and nonspatial abilities and reference and working memory deteriorate with age – an effect that is antagonized with life-long CR (Pitsikas and Algeri, 1992). Similar studies in mice revealed that chronic CR enhances their learning ability and memory (Hashimoto and Watanabe, 2005; Komatsu et al., 2008; Kuhla et al., 2013; Wahl et al., 2018). One of the mechanisms proposed to explain the beneficial effects of CR on cognitive aging is through changes in neurogenesis. Studies in rodents (reviewed in Arslan-Ergul et al., 2013 and Stangl and Thuret, 2009) found that CR increases AHN (Hornsby et al., 2016). However, it still is not established if this occurs through an increase in cell survival (Lee et al., 2002, 2000), through an increase in NSC proliferation (Kaptan et al., 2015; Park et al., 2013) or both. Furthermore, CR not only enhances proliferation of NSCs in young mice, but also prevents the age-related loss of neurogenesis in the SVZ – an effect associated with an improvement in olfactory memory (Apple et al., 2019).High-fat diet (HFD) has an opposite effect in both mice and rats, impairing hippocampal neurogenesis and proliferation of NSCs (Lindqvist et al., 2006; Park et al., 2010). Interestingly, this effect might be transgenerational, as it was shown that HFD-induced maternal obesity could impair AHN during postnatal development of the offspring (Tozuka et al., 2009). In humans, a randomized clinical trial with long-term CR (25% reduction during 2 years) found positive effects on working memory in healthy individuals (Leclerc et al., 2019). An interventional trial in elderly subjects found that 3 months of CR (reduction of 30% relative to previous habits) had beneficial effects on memory performance (Witte et al., 2009). The same group carried out a study in healthy obese postmenopausal women and found that a CR intervention (12-week low-caloric diet) was able to improve recognition memory, an effect that was specific for the weight loss phase that could not be detected in the subsequent weight maintenance phase (Prehn et al., 2016). This effect was associated with an increase in gray matter volume in the hippocampus (as well as the inferior frontal gyrus) and augmented hippocampal resting-state functional connectivity to parietal areas (Prehn et al., 2016). While these studies suffer from certain limitations (self-reporting being one), their findings support the data from experimental animal studies (mentioned above) and epidemiological studies in humans (Mattson, 1999; Parrott and Greenwood, 2007). It is known that CR can enhance neurogenesis in the animal DG, and a recent study in obese adults has shown that CR may influence memory function through modulating AHN (Kim et al., 2020). Further clinical research is needed to determine if CR has a direct effect on the aging DG, and in which groups of people it has the highest efficiency. For example, CR could work well in overweight people, but have limited benefits, or even adverse effects such as dysmenorrhea (Romashkan et al., 2016), in healthy young people.

4.2. Pharmacological approaches

There are different pharmacological compounds that have been shown to stimulate neurogenesis (set A), to protect against neurodegeneration (set B) and to extend lifespan (set

C). In this review, we will focus on those found at the intersection of all three sets. We have further narrowed our criteria to compounds that (1) have been extensively researched and that (2) target different metabolic pathways. With that in mind, the compounds whose effects we will describe in this section are: NAD$^+$ (nicotinamide adenine dinucleotide)-boosting molecules (NBMs), resveratrol, rapamycin and metformin.

The effect of these compounds on lifespan and healthspan is heterogenous, and will be briefly summarized here. NBMs extended the lifespan of mice in some studies (Fang et al., 2016; Zhang et al., 2016), had no effect on it in others (Harrison et al., 2021; Mitchell et al., 2018), and seem to have a positive effect on healthspan (Mitchell et al., 2018), The therapeutic potential of some NBMs has been thoroughly reviewed elsewhere (Yoshino et al., 2018), but long-term clinical studies are needed to establish their safety and physiological outcomes. Resveratrol was able to extend the lifespan of some simpler organisms such as nematodes or fruit flies (Bauer et al., 2004; Wood et al., 2004), but not in mice or rats. While the effects on lifespan are unclear, we decided to include resveratrol in the review because of its beneficial effects on mammal healthspan and because of an excellent safety profile (Bhullar and Hubbard, 2015; Pezzuto, 2019), making it a lower-risk intervention that might have positive effects on certain health indices. The data is much clearer with rapamycin, which can extend lifespan in organisms ranging from yeast and flies to mice, recently summarized in (Selvarani et al., 2021). Additionally, it can also improve healthspan in mice (Bitto et al., 2016; Zhang et al., 2014) and has low toxicity in humans (Ceschi et al., 2015), making it overall a good candidate for geroscience-focused clinical trials. Lastly, the effects of metformin on lifespan are inconclusive and depend on the model organism, sex and dose used. While some studies show a positive effect on lifespan extension (recently reviewed in (Hu et al., 2021)), a study from the Interventions Testing Program found no effect on median or maximum lifespan (Strong et al., 2016). However, it does seem to improve healthspan (recently reviewed in (Mohammed et al., 2021), and clinical trials such as MILES and TAME will help answer questions about the potential prophylactic usage of metformin to counteract certain effects of aging itself.

NAD$^+$-boosting molecules—NBMs that we will focus on are nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR). NR is the precursor to NMN, which is in turn one of the precursors to NAD$^+$ - a molecule that is essential for a myriad of enzymatic processes whose levels decline with aging (Imai and Guarente, 2014). There is a profound connection between NAD$^+$ and sirtuins, which are deacetylase enzymes that regulate numerous fundamental biological processes implicated in both lifespan and neurodegenerative diseases (Alcaín and Villalba, 2009; Fang et al., 2017; Imai and Guarente, 2016).

It has been shown that NMN supplementation improves cognitive function in aged mice (Tarantini et al., 2019) and alleviates aging-induced cognitive impairment in rats while reducing apoptosis in the prefrontal cortex and hippocampus (Hosseini et al., 2019). Systemic NMN administration was able to rescue the aging-associated decline of the NSC pool in mice, but not to drive the proliferation of these aged NSCs (Stein and Imai, 2014). Similarly, in a mouse model of cerebral ischemia, delayed administration of NMN improved regenerative neurogenesis in both the SVZ and DG (Zhao et al., 2015). Similar results were

observed with NR: its administration was able to increase neurogenesis in the SVZ and DG in aged mice, while at the same time slightly increasing lifespan (Zhang et al., 2016). The same effect on lifespan wasn't observed in a transgenic mouse model of amyotrophic lateral sclerosis (ALS) (SOD1^{G93A} mice), but improvements in neurogenesis were observed: NR was able to attenuate the ALS-induced loss of NSCs in the SVZ, SGZ and OB, as well as to enhance the proliferation and migration of NSCs (Zhou et al., 2020). In a model of AD (3xTgAD/Polβ$^{+/−}$ mice), 3 months of NR treatment (in animals that were 16 to 18 months old) was able to reduce neuroinflammation, increase NSC proliferation, decrease tau phosphorylation in the hippocampus as well as improve learning, memory and motor function (Hou et al., 2018). Similar effects were found in the APP/PS1 mouse model of AD, where the same length of NR treatment improved memory and learning in mice 7 to 12 months old, but the effects on neurogenesis were not assessed (Hou et al., 2021). Interestingly, some of these effects seem to be transgenerational, as rats nursed by NR-fed mothers display enhanced hippocampal neurogenesis as adults, as well as advantages in spatial memory and physical performance (Ear et al., 2019).

Resveratrol—Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene; RSV) is a polyphenolic phytoalexin that is generated in response to stress in specific plants such as grapevines (Bhat et al., 2001). RSV has been classified by some as a sirtuin-activating compound (STAC) and has been suggested to be a caloric restriction mimetic (CRM) (Nikolai et al., 2015). However, we note that some studies suggested that resveratrol does not directly activate SIRT1, a protein which was suggested to be its primary target (Pezzuto, 2019).

RSV administration improves performance in behavioral tests related to memory formation and promotes the survival of newborn hippocampal cells in BALB/c mice at 6 months of age (Torres-Pérez et al., 2015). Similarly, adding RSV to HFD-fed mice positively affected adult hypothalamic neurogenesis, both by its anti-apoptotic effect and through enhancing production of newborn cells in the arcuate nucleus of the hypothalamus (Safahani et al., 2019). In mice exposed to neonatal hypoxic ischemia, RSV could prevent cognitive deficits by promoting AHN (Li et al., 2020). In rats exposed to unpredictable chronic mild stress (UCMS), RSV was able to reverse UCMS-induced impaired cognition function and improve hippocampal expression of BDNF, a key molecule in regulating hippocampal plasticity (Yazir et al., 2015). In late middle-age (21 months) male F344 rats, RSV administration improved learning, memory and mood function, as well as increased neurogenesis in the DG (Kodali et al., 2015). Lastly, RSV administration enhanced AHN in rats exposed to lead early in life, which had a protective effect against learning and memory impairments induced by lead neurotoxicity (Wang et al., 2021).

In humans, a double-blind placebo-controlled study with chronic RSV supplementation (200 mg per day for 6 months; in a formula with quercetin) found positive effects on memory performance in healthy overweight older adults, a finding associated with increased hippocampal functional connectivity (Witte et al., 2014). Moreover, a similar study carried out in patients with mild cognitive impairment (MCI) found that the same dose and duration of RSV supplementation had no significant effects on memory performance, but could preserve hippocampal volume and improve hippocampus resting-state functional connectivity (Köbe et al., 2017). Another study utilizing the same dose and duration of

RSV supplementation in healthy elderly individuals failed to find improvements in verbal memory, finding only a trend for positive effects on pattern recognition memory (Huhn et al., 2018). In a shorter study utilizing a lower dose of RSV (150 mg per day for 14 weeks) in postmenopausal women, it improved verbal memory and overall cognitive performance (Evans et al., 2017). In healthy young adults (18–30 years), chronic administration of RSV (500 mg per day for 28 days) was not able to improve cognitive function (Wightman et al., 2015). Finally, a meta-analysis exploring the effect of RSV on cognitive and memory performance concluded that chronic RSV supplementation has no significant impact on those indices (Farzaei et al., 2018). In summary, despite promising effects on neurogenesis in animals, it is difficult to firmly conclude if supplementing humans with RSV increases AHN or if it confers advantages in cognitive and memory performance. Further studies with a longer intervention period and larger sample sizes are needed.

Rapamycin—Rapamycin is a macrolide that directly and specifically inhibits the mechanistic target of rapamycin (mTOR), a nutrient-responsive kinase that is the catalytic subunit of two complexes known as mTOR complex 1 (mTORC1) and as mTOR complex 2 (mTORC2). It has been established that while rapamycin directly inhibits mTORC1, mTORC2 is not sensitive to acute rapamycin treatment and chronic exposure is required to indirectly inhibit mTORC2 (Arriola Apelo and Lamming, 2016). Many of the side effects of prolonged rapamycin treatment, such as immunosuppression and glucose intolerance, are considered due to the inhibition of mTORC2, so inhibitors that are specific to mTORC1 might confer beneficial effects while avoiding the side effects (Saxton and Sabatini, 2017). Rapamycin has been proposed as a CRM (Hughes and Kennedy, 2012), but some researchers believe that it is likely that rapamycin and CR exert their effects through different pathways (Unnikrishnan et al., 2020).

Treatment with rapamycin has been associated with improvements in learning and memory in both young and old animals. In 8-month-old male mice, chronic rapamycin treatment (16 weeks) was able to enhance spatial learning and memory, as well as reduce anxiety- and depression-like behaviors (Halloran et al., 2012). The same study observed that 40 weeks of treatment improved recall of an aversive event in older mice (25 months of age), suggesting that even when started late in life, chronic rapamycin treatment was able to delay cognitive decline associated with aging (Halloran et al., 2012). Similarly, lifelong rapamycin administration in mice (started at 2 months of age) was able to improve learning and memory when tested at 18 months of age, but shorter rapamycin administration in adult mice (12 weeks; started at 15 months of age) wasn't able to improve cognition in animals with pre-existing, age-dependent learning and memory deficit (Majumder et al., 2012). Finally, chronic treatment (15 months) with rapamycin was able to ameliorate deficits in learning and memory in aged (34-month old) rats (Van Skike et al., 2020). Hence, it is yet to be determined which dosing and duration at which age are optimal for exerting improvements in cognitive function. Interestingly, 12 weeks of rapamycin administration in 22-month old mice resulted in increased abundance of activated NSCs in the SVZ (Leeman et al., 2018). However, different results were obtained in a study where rapamycin (i.p.) significantly reduced the number of proliferating cells in the adult hippocampus of 3-month old mice (Romine et al., 2015). It is difficult to compare these results as (1) the experiments

were carried out in different age groups, (2) the method and duration of rapamycin administration was different and (3) as they focus on different neurogenic niches. Hence, further experiments are necessary to determine the effects of rapamycin on neurogenesis - especially in the DG of healthy mice after prolonged administration. In humans, a small study in heart transplant recipients found that short-term (4 weeks) immunosuppression with a rapamycin analogue everolimus was associated with improvements in memory performance and mood (Lang et al., 2009). However, a randomized controlled trial in healthy older adults (25 subjects) revealed no improvements in cognition after 8 weeks of rapamycin treatment, noting that longer trials with larger sample sizes may be warranted (Kraig et al., 2018). A clinical trial exploring the effects of rapamycin in older adults with MCI on cognition is currently active (NCT04200911).

Metformin—Metformin (*N,N*-dimethylbiguanide) is an anti-diabetic drug that inhibits the mitochondrial respiratory chain complex I, leading to multiple downstream effects such as changing the AMP:ATP and ADP:ATP ratios, which activates AMP-activated protein kinase (AMPK) (Barzilai et al., 2016; Rena et al., 2017). Metformin also inhibits hepatic mTORC1 in a biphasic manner: low dose of metformin requires AMPK and the TSC complex for the inhibition, whereas a high dose inhibits mTORC1 through alternative mechanisms, independently of AMPK and TSC complex (Howell et al., 2017). While it has been argued that metformin acts as a CRM (Kezic et al., 2018), results from other model organisms such as *Drosophila* and mammals call that into question (Lee and Min, 2013; Slack et al., 2012).

Most (but not all) studies have found a positive effect of metformin on cognitive functions and neurogenesis, both in metabolically compromised and in aged animals. In a mouse model of diabetes induced by streptozotocin, metformin treatment produced an improvement in spatial memory and a decreased loss of neurons in the DG of diabetic mice (De Oliveira et al., 2016). Similar effects were observed in a study by Wang et al. in 2012, who reported that metformin administration enhanced spatial memory formation and promoted neurogenesis in both the SVZ and the SGZ of mice, without depleting the endogenous NPC pool. In a transgenic mouse model of AD (APP/PS1 female mice), 14 days of daily metformin treatment rescued spatial memory deficits, reduced brain Aβ deposition and Aβ levels, prevented neuronal cell death in the hippocampus as well as increased AHN (Ou et al., 2018). Similarly, in 3xTg-AD mice, the same length of metformin treatment rescued impairments in AHN and spatial memory (Syal et al., 2020). It was observed that metformin enhances the proliferation, self-renewal, and neuronal differentiation of adult NPCs through two distinct molecular pathways: a TAp73 pathway mediating self-renewal and proliferation, and an AMPK-aPKC-CBP pathway that is required for metformin-induced neuronal differentiation (Fatt et al., 2015). In HFD-induced insulin resistant rats, metformin restored the learning and memory behaviors that were impaired by long-term HFD consumption (Pintana et al., 2012). Similarly, in HFD-fed obese mice, metformin had a beneficial effect on learning and memory, and also restored impairments in AHN, through the regulation of gut microbiota (Ma et al., 2021). 36 days of metformin administration enhanced the spatial memory of aged rats in the Morris Water Maze (Ashrostaghi et al., 2015). In a D-galactose-induced aging model in mice, metformin administration improved learning and memory ability, assessed by the novel object recognition task (Fatemi et al., 2018). However,

one study found no beneficial effect of metformin supplementation on learning in old male mice – in fact, metformin exhibited a deleterious effect on memory retention (Thangthaeng et al., 2017). Metformin use was also associated with impaired cognitive performance in patients with diabetes (Moore et al., 2013), but another study in diabetic individuals showed that metformin treatment was inversely related to cognitive impairment (Ng et al., 2014). In summary, many studies show that metformin improves neurogenesis in various animal models, and is a promising candidate against cognitive impairments in humans. Hence, future research should address the interaction of effects of metformin on cognitive functions with age, sex, dosage, and duration of treatment.

5. Conclusions

We have discussed some alterations of adult neurogenesis in aging and neurodegenerative diseases in this review. The dysfunction of AHN appears to be an early marker of the development of these aging-related diseases and it seems that the regulation of neurogenesis could be an effective intervention against them.

The iPSC technology is widely used to screen anti-neurodegenerative drugs and understand the mechanisms of mutations involved, which could recapitulate the dynamic processes of neurogenesis *in vitro* (Chen et al., 2020). In addition, iPSCs can be used as the autologous source for stem cell therapy. Transplantation of NSCs is regarded as a prospective therapeutic intervention (De Gioia et al., 2020). In the past few decades, many promising preclinical and early clinical findings of stem cell therapy were obtained from animal models (Ford et al., 2020). However, the risk of teratoma formation and mutations, as well as the optimization of stem cell sources and procedures, continue to be the major issues for further feasible and safe applications, which must be solved (Itakura et al., 2017; Merkle et al., 2017). Therefore, a more in-depth knowledge of the characteristics of NSCs and the related neurotrophic factors and differential stimulations, as well as how to combine genetic engineering like CRISPR/Cas9 and RNAi to modify patient-derived iPSCs for autologous transplantation, will help us tackle the obstacles.

It should also be noted that increasing AHN beyond physiological levels might have harmful effects. While deficits in plasticity are associated with certain disorders and could leave the brain unable to adjust to changing demands, so could a supraphysiological increase in AHN result in maladaptive effects, with structural connections becoming unstable, resulting in compromised cognition and behavior (Pascual-Leone et al., 2011). For example, increasing the number of adult-born cells by blocking cell death in the OB impairs performance in odor discrimination tasks (Mouret et al., 2009). Furthermore, it was shown that adult neurogenesis transiently generates oxidative stress, which has been implicated in a wide variety of CNS disorders (Walton et al., 2012). There is likely a point where the balance between plasticity and stability (neuronal turnover) is at its optimal value for cognition and overall brain health, and further research is needed to determine if there is a threshold at which point too many new neurons become deleterious. Similarly, since AHN can be divided into stages of proliferation, migration and differentiation, strategies targeting different components could be utilized in different conditions. It has been suggested that for MDD and some other conditions that involve the hippocampus, neurogenesis could be

induced, while for PD and HD, the optimal strategy would be to induce the local dividing cells to proliferate and then differentiate into small spine neurons (for HD) or dopaminergic neurons (PD) (Gage, 2004).

A similar cost-benefit analysis should be carried out for other manipulations mentioned in the review. For example, NAD^+ is a ubiquitous biological molecule that is central to several cellular bioenergetic functions and is used as a cofactor or substrate by hundreds of enzymes (Covarrubias et al., 2021; Lautrup et al., 2019) and, as such, levels of caution should be used in employing system-wide manipulations. Potential risks and benefits of NBMs have been reviewed comprehensively elsewhere (Braidy and Liu, 2020), so we will only briefly mention some of the potential negative consequences. For instance, cancer cells, being highly replicative, have a high energy demand and thus NAD^+ supplementation could promote the growth of specific cancers by fueling cell proliferation (Demarest et al., 2019; Lautrup et al., 2019). It has been shown that NMN supplementation can promote the proinflammatory senescence-associated secretory phenotype (SASP), which has tumorigenic properties (Nacarelli et al., 2019). The authors suggest that NAD^+ should be supplemented with precision to balance the advantageous "anti-aging" effects with potential detrimental pro-tumorigenic side-effects (Nacarelli et al., 2019). We suggest that the potential negative effects of the SASP might also be offset by combinational therapy – for example, administering NBMs after clearing senescent cells with senolytics has the potential to synergize. More recently, a study which utilized an NR washout phase in its experimental design showed that the beneficial effects of NR are not sustained after its removal in aged animals, and that removing NR might have undesirable consequences (Zong et al., 2021). The authors conclude that the supplementation regimen may need to be sustained long-term to maintain its benefits, and we argue that further studies with washout periods in aged animals are necessary to ascertain organism-wide effects of cessation of NR supplementation.

The potential shortcomings of utilizing system-wide (mTOR, AMPK, sirtuins) manipulations should be explored in detail. Optimal levels of these manipulations should be determined, their interactions in a form of combinatorial therapy, as well as methods to precisely target dysfunctional systems. Despite potential shortcomings, the currently available data suggests that modulating neurogenesis represents an important target for manipulations that could help in the fight against neurodegenerative disorders and cognitive decline, ultimately leading to improvements in both lifespan and healthspan.

Abbreviations

Aβ	amyloid beta
AD	Alzheimer's disease
AHN	adult hippocampal neurogenesis
APOE	apolipoprotein E
A-T	Ataxia Telangiectasia

ATM	Ataxia Telangiectasia mutated
BDNF	brain-derived neurotrophic factor
BER	Base excision repair
BrdU	Bromodeoxyuridine
CDC42	Cell division control protein 42 homolog
CNS	central nervous system
CR	caloric restriction
CS	Cockayne syndrome
DCX	Doublecortin
DG	dentate gyrus
DNAJC6	DnaJ Heat Shock Protein Family (Hsp40) Member C6
DSB	DNA double-strand break
EE	Environmental enrichment
EOAD	early-onset Alzheimer's disease
FBXO7,	F-Box Protein 7
GABA	gamma-aminobutyric acid
γH2AX	gamma H2A histone family member X
HD	Huntington's disease
ihNSC	immortalized human neural stem cell line
LB	Lewy body
LOAD	late-onset Alzheimer's disease
LRRK2	Leucine Rich Repeat Kinase 2
MCI	mild cognitive impairment
NAD$^+$	nicotinamide adenine dinucleotide
NEIL1	Nei Like DNA Glycosylase 1
NEIL3	Nei Like DNA Glycosylase 3
NER	Nucleotide excision repair
NPC	Neural progenitor cell
NSC	neural stem cell

OB	olfactory bulb
PCNA	proliferating cell nuclear antigen
PD	Parkinson's disease
PE	Physical exercise
PINK1	PTEN Induced Kinase 1
Polβ	DNA polymerase β
poly Q	polyglutamine
PRKN	parkin RBR E3 ubiquitin protein ligase
PS1	presenilin 1
PS2	presenilin 2
RMS	rostral migratory stream
RSV	Resveratrol
SGZ	subgranular zone
SNCA	synuclein alpha
SOX2	sex determining region Y-box 2
SVZ	subventricular zone
VEGFA	vascular Endothelial Growth Factor A
VPS35	VPS35 Retromer Complex Component

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Highlights

- Formation of new neurons (neurogenesis) plays a significant role throughout lifespan

- The incidence of neurodegeneration increases with aging, while neurogenesis decreases

- Age-associated decline in brain function may be caused by neural stem cell defects

- Geroscience interventions that target the aging process mostly enhance neurogenesis

- Enhancement of neurogenesis is beneficial in aging and neurodegeneration

- Optimal levels of neurogenesis induction and adverse effects should be determined
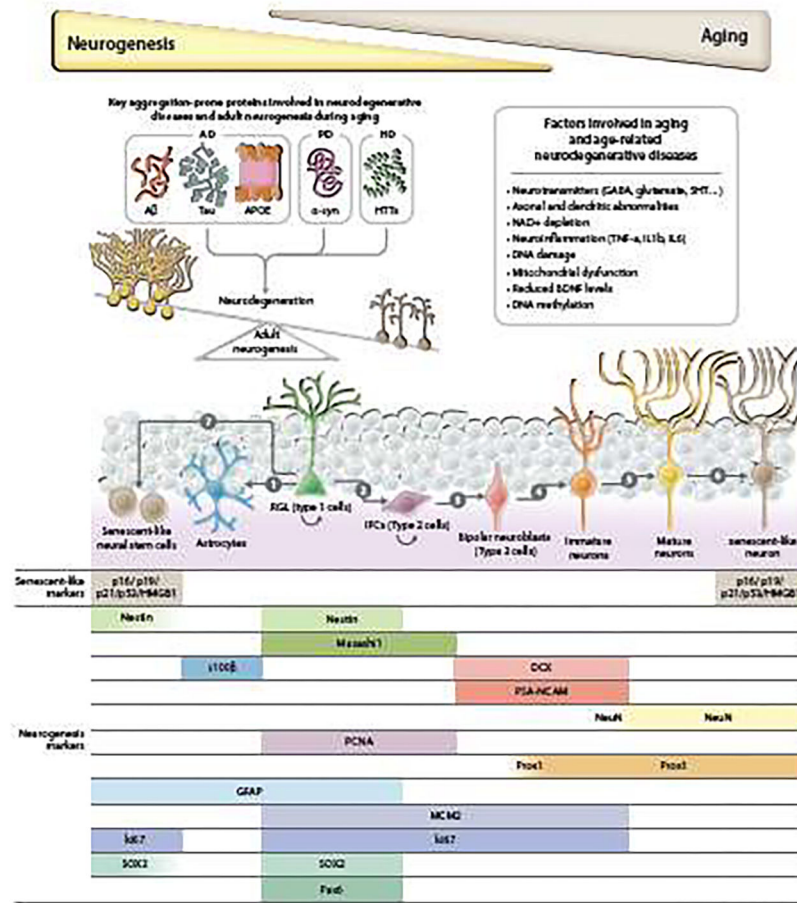
Figure 1. Key aggregation-prone proteins involved in neurodegenerative diseases and adult hippocampal neurogenesis during aging

Adult hippocampal neurogenesis decreases with aging. Aggregation-prone proteins, like Aβ, tau and APOE in AD, α-syn in PD and HTTs in HD accumulate during the aging process and induce neurodegeneration as well as impair hippocampal neurogenesis, resulting in the imbalance between these two processes. Various factors that are tightly connected with neurogenesis are involved in the pathologies of aging and neurodegenerative diseases and are discussed in this review. In the hippocampus, the process of neurogenesis starts with radial glia-like (RGL) cells (type 1 cells). The RGL cells keep self-renewing and give rise to astrocytes (1) and intermediate progenitor cells (IPCs or type 2 cells) (2). IPCs proliferate and differentiate into bipolar neuroblasts (3). Those neuroblasts differentiate into immature neurons (4). Then these immature neurons undergo a dynamic maturation process, with some of them dying, and some surviving to become mature neurons and form functional connections to existing neural networks (5). Several studies have demonstrated that markers of senescence, like p16, p19, p53 and HMGB1, are increased in some neurons and neural stem cells (6 &7) (Molofsky et al., 2006; Negredo et al., 2020; Nicaise et al., 2019). This age-associated NSC senescence could result in the depletion of NSCs, ultimately decreasing adult hippocampal neurogenesis and impairing brain function. At the bottom is the schematic of specific markers expressed during hippocampal neurogenesis and senescence.
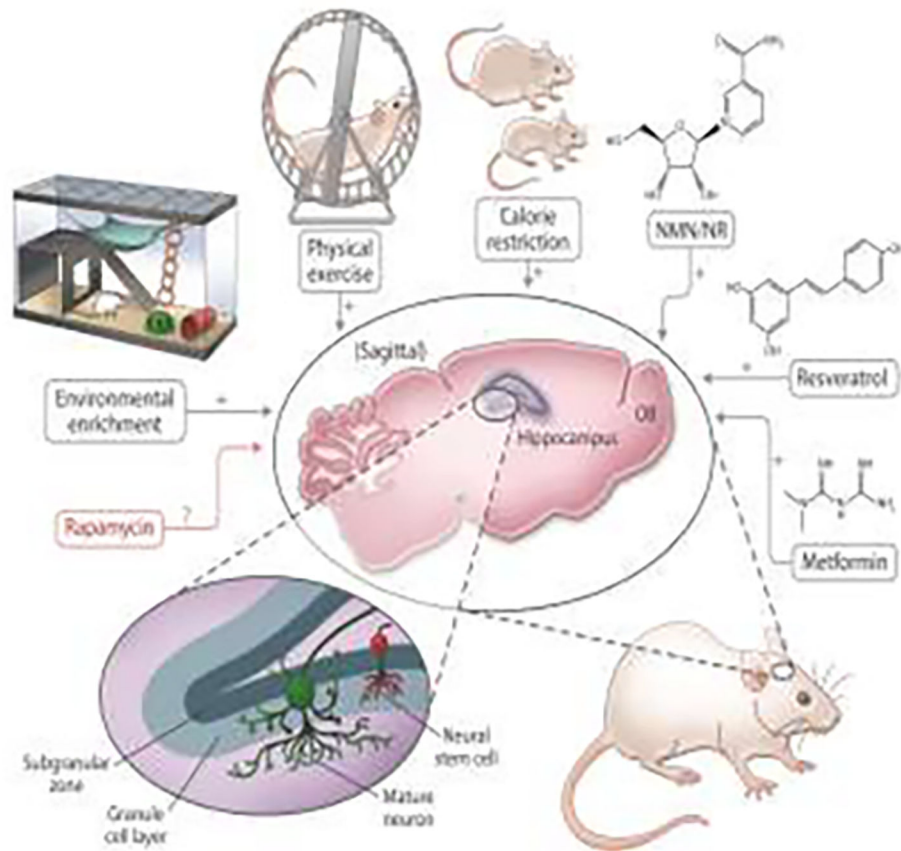
Figure 2. The effects of certain life/healthspan interventions on adult neurogenesis in rodents.
This illustration encapsulates the effects of several common life/healthspan manipulations on adult neurogenesis in rodents, which are described in this review. Environmental enrichment, physical exercise, calorie restriction, NAD-boosting molecules (NMN/NR), resveratrol and metformin all increase neurogenesis in animal models, while the effects of rapamycin have not yet been comprehensively established in that regard.

Table 1-

Summary of studies on the changes of neurogenesis in animal models of neurodegenerative diseases.

Here we summarized previous studies on the changes of neurogenesis in both SGZ and SVZ in animal models of neurodegenerative disorders, including the type of animal model, investigated area and markers used in studies, as well as the details of phenotypes related to neurogenesis. Altered neurogenesis was found in most of these animal models, which may contribute to the etiology involved in neurodegenerative diseases.

Disease	Organism	gene	Area	Change in neurogenesis	Markers	Age(month)	Features related to neurogenesis	Refs
AD	Mouse	$APP_{S\,w,Ind}$	SGZ	↑	BrdU, Ki67, PSA-NCAM, β-tubulin III	3	Increased BrdU$^+$, Ki67$^+$ cells by increased neuronal differentiation labeled by PSA-NCAM$^+$, β-tubulin III$^+$ cells;	(López-Toledano and Shelanski, 2007)
				↓		5, 9, 11	Reduced neurogenesis started at 5-month-old and persisted at 9- and 11 month-old.	
		APP	SGZ	N.C.	DCX, MCM2, NF68	8–9, 18–24	No change in DCX$^+$ cells	(Zhang et al., 2007)
		PS1	SGZ	↓			A small decrease in DCX$^+$ cells	
		APP, PS-1	SGZ	↓			Reduced by 60% and in an age dependent way	
		APPswe, PS1-dE9	SGZ	↑	BrdU, DCX	3, 9	The memory and hippocampal proliferation were not affected at 3-month-old; Memory impairment, increased Aβ deposits, and	(Yu et al., 2009)
Disease	Organism	gene	Area	Change in neurogenesis	markers	Age (month)	Features related to neurogenesis	Refs
AD	Mouse	APP, PS1, nestin-GFP	SGZ	↓	nestin-GFP DCX BrdU GFAP	7d, 1, 3, 7	BrdU$^+$-, DCX$^+$- and GFAP$^+$- Nestin-GFP$^+$ cells decreased started from 3 month-old. Abnormal morphologies of dendrites in SGZ;	(Zeng et al., 2016)
			SVZ	N.C.			The number of nestin-GFP$^+$ cells decrease	
		PS1HWT	SGZ and SVZ	N.C.	BrdU	2	No change in BrdU$^+$ and DCX$^+$ cells	(Demars et al., 2010)
		APPs we, PS1 E9	SGZ	↓	BrdU DCX	2	Reduced as early as 2 month-old; impaired proliferation and tau hyperphosphorylation exhibited in neurospheres isolated from	
			SVZ	↓				

Disease	Organism	gene	Area	Change in neurogenesis	markers	Age (month)	Features related to neurogenesis	Refs
							APPswe/PS1 E9 mice	
AD	Mouse and NPCs	*APPswe, PS1 E9*	SGZ	-	EdU	4	Transplantation of human NPC reduced Aβ load and increased microglia within hippocampal and cortical regions; Improve hippocampal dependent cognition	(McGinley et al., 2018)
Disease	**Organism**	**gene**	**Area**	**Change in neurogenesis**	**markers**	**Age (month)**	**Features related to neurogenesis**	**Refs**
AD	Mouse and NPCs	*APP$_{KM670/671NL}$*	SVZ	↓	BrdU, DCX, SOX2, GFAP	1.5	Decreased OB neurogenesis and fewer Calretinin$^+$ interneurons in OB; Smaller neuron size; More DCX$^+$ neuroblasts and fewer Sox2$^+$ progenitors	(Scopa et al., 2020)
		Aβ	SGZ	↓	GFAP, Ki67, CD44, CD90, CD34, CD45	1.5	Aβ-treated NPCs decreased the expression of Ki67, GFAP, SOX2, and Nestin by suppressing the Wnt signaling pathway	(Oh et al., 2015)
	Rat	*Aβ*	SGZ	-	-	P5,P7,P15,P25	Aβ trigger spine loss by partially inhibiting NMDARs	(Shankar et al., 2007)
	Mouse	*MAPT*	SGZ	↓	DCX, Ki67	2, 6, 12	Decreased Dcx-NeuN$^+$ cells as early as 2 months of age in both SGZ and SVZ; Decreased Ki67$^+$ cells in SVZ with aging	(Komuro et al., 2015)
			SVZ	↓				
			-	-	-	6	Aging-dependent short-term memory deficits, hyperactivity and synaptic plasticity defects	(Biundo et al., 2018)
Disease	**Organism**	**gene**	**Area**	**Change in neurogenesis**	**Markers**	**Age (month)**	**Features related to neurogenesis**	**Refs**
AD	Mouse	*Tau Tg30*	SGZ	↓	DCX, Ki67, GFAP	12	DCX$^+$ and Ki67$^+$ cells decreased in Tg30 mice but not in Tg30/tau KO mice; GFAP$^+$ cells showed no difference between Tg30 and Tg30/tau KO mice	(Houben et al., 2019)
		Tg30/TauKO						
		APPswe, PS1$_{M146V}$, MAPT$_{P301L}$	SGZ	↓	HH3	2–4, 6, 9, 12	The age-associated reduction was more significant in female mice; More related to dorsal than ventral hippocampus	(Rodríguez et al., 2008)
		APPswe, PS1$_{M146}$, MAPT$_{P301L}$, Polβ	SGZ	↓	BrdU	6, 14	No change in hippocampal volume and adult neurogenesis at 6 months, but reduced at 14 months; Impaired	(Sykora et al., 2015)

Disease	Organism	gene	Area	Change in neurogenesis	label	Age (month)	Features related to neurogenesis	Refs
							memory and synaptic plasticity in 3xTg/Pol $\beta^{+/-}$ mice	
		5xFAD	SGZ	↓	DCX, HH3, calretinin	2–4, 7	The number of DCX[+], HH3^{+}, and calretinin [+] cells decreased in 5xFAD hippocampus;	(Moon et al., 2014)

Disease	Organism	gene	Area	Change in neurogenesis	label	Age (month)	Features related to neurogenesis	Refs
AD	Mouse	5xFAD	SGZ	↓	Ki67, DCX, SOX1, SOX2, SOX21	2	SOX1[+] and SOX21^{+} cells decreased in AD mice; DCX^{+} cells decreased only in male AD mice; SOX2^{+} cells decreased only in female AD mice; No change in the Ki67^{+} cells in both gender; The protein levels of BDNF were not affected in the 5xFAD mice	(Zalet el et al., 2018)
		5xFAD	SGZ	↓	DCX	10	Reduced neuron numbers and neurogenesis both in males and females; Restored by overexpression of VGF, a nerve growth factor	(Beckmann et al., 2020)
		PS1	ventricular zone	↓	BrdU	E11.5	Premature differentiation of NPCs, which leading to early depletion of the neural progenitor population	(Yang et al., 2000)
		PS2		N.C.	DCX, Ki67	1.5–2	Deletion of PS2 does not affect hippocampal adult neurogenesis	(Dhaliwal et al., 2018)

Disease	Organism	gene	Area	Change in neurogenesis	label	Age (month)	Features related to neurogenesis	Refs
AD	mouse	APOE ε3/ APOE ε4	SGZ	↓	Nestin, SOX2, BrdU, GFA P	3, 6–7, 12–13	Neurogenesis reduced but astrogenesis increased in APOE-KO Mice; Increased BMP signaling promoted glial differentiation at the expense of neurogenesis in APOE ε4 mice, Presynaptic GABAergic input-mediated maturation of newborn neurons was diminished in APOE ε4 mice	(Li et al., 2009)
			SVZ	↓				
		GFAP-APOE	SGZ	↓	BrdU, GFAP	2	Reduced APOE after injury; The injury-induced proliferation of hippocampal neural progenitors is absent	(Hong et al., 2016)

Disease	Organism	gene	Area	Change in neurogenesis	label	Age (month)	Features related to neurogenesis	Refs
							in APOE-deficient mice; GFAP-ApoE4 mice decreased neurogenesis after injury.	
		nestin-APOE	SGZ	↓	DCX	1, 2, 9	An overall decrease in type 1 Nestin- and GFAP-expressing neural stem cells	(Yang et al., 2011)
		GFAP-APOE	SGZ	N.C.	synaptophsin, NSE, GFAP	6, 10, 14	Impaired learning and working memory; Increased activity and anxiety; no alterations of the expression synaptophysin, NSE, GFAP	(Hartman et al., 2001)
Disease	**Organism**	**gene**	**Area**	**Change in neurogenesis**	**label**	**Age (month)**	**Features related to neurogenesis**	**Refs**
A-T	Mouse and NPCs	*ATM*	-	-	Ki67, GFAP	3	No change in the number of proliferating cells; Resistance to apoptosis after irradiation	(Barazzuol et al., 2017)
	Mouse		SGZ	↑	Ki67, EdU, cyclin A, PCNA	2, 3	Neurons loss in hippocampus and frontal cortex; Cyclin A[+] and PCNA^{+} cells were significantly elevated	(Shen et al., 2016)
			SGZ	↓	BrdU	1, 2	ATM down regulated during cells differentiate; Decreased proliferation and survival of NPCs and genomic instability	(Allen et al., 2001)
PD	*C. elegans*	*SNCA*	-	↓	-	-	Neuronal and dendritic loss in dopaminergic neurons but not with a motor neuron promoter	(Lakso et al., 2003)
	Mouse		SVZ	↓	PCNA, DCX+ BrdU	5, 15	Decreased number of PCNA[+], DCX[+] and BrdU^{+} cells and increase in TUNEL^{+} cells in OB	(Winner et al., 2008)
		Lrrk2	SGZ	↓	DCX, BrdU	4	Decreased proliferation both in SGZ and SVZ Neurite outgrowth and spine numbers reduced in new neurons in DG	(Winner et al., 2011)
			SVZ	↓				
Disease	**Organism**	**gene**	**Area**	**Change in neurogenesis**	**label**	**Age(month)**	**Features related to neurogenesis**	**Refs**
PD	Mouse and NPCs	*PINK1 (PARK6)*	SGZ	↓	DCX, SOX2	3	Decreased proliferation and TMRE/Mi toTracker Green ratio; Reduced maximum OCR, spare respiratory capacity and growth; Increased apoptosis	(Agnihotri et al., 2017)

							in PINK1⁻/⁻ NSCs; Abnorma l morpholo gic features of PINK1⁻/⁻ DCX⁺ neurons	
		Parkin (PARK2)	SVZ	↓	GFAP	E15	Arrested neuronal differentiation and abnormal morphology of NPCs; Decreased GFAP⁺ cells	(Park et al., 2017)
	Rat	SNCA	SGZ	↓	BrdU	4	Reduced survival of BrdU⁺ cells in DG, while proliferation not be affected	(Kohl et al., 2016)
CS	Human iPSC	CSB	-	↓	PAX6, OCT4, SOX2	-	Reduced differentiation potential and proliferati on	(Vessoni et al., 2016)
	Mouse	CSB	SGZ	N.C.	BrdU	E14.5, 4	Neural progenitors were not affected but showed defective self-renewal	(Sacco et al., 2013)

Abbreviations: ↑, increase; ↓, decrease; Aβ, amyloid beta; AD, Alzheimer's disease; APOE, apolipoprotein E; APP, amyloid precursor protein; A-T, Ataxia Telangiectasia; ATM, Ataxia Telangiectasia mutated; BDNF, brain-derived neurotrophic factor; BrdU, Bromodeoxyuridine; DCX, Doublecortin; DG, dentate gyrus; E, embryo; NSC, neural stem cell; OB, olfactory bulb; P, postnatal day; PCNA, proliferating cell nuclear antigen; PD, Parkinson's disease; Polβ, DNA polymerase β; PS1, presenilin 1; PS2, presenilin 2: SGZ, subgranular zone; SNCA, synuclein alpha; SOX2, sex determining region Y-box 2; SVZ, subventricular zone