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Young at heart: Insights into hippocampal neurogenesis in the aged brain

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Abstract

While the existence and importance of adult hippocampal neurogenesis in young adult rodents has been well-established, such qualities in aged animals and humans have remained poorly understood. Most evidence in humans has come from hippocampal volumetric changes that provide no direct proof of new neurons in adulthood. Here, we review the basic neurobiological evidence for adult hippocampal neurogenesis in the aged brain of experimental animals with short and long lifespans, and humans. The rate of cell cycling and addition of new hippocampal neurons to the existing hippocampal circuit undoubtedly decreases with age. Yet, neural stem/progenitor cells that persist into senescence may activate and produce a substantial number of functional new neurons that exhibit enhanced survival and integration given the right set of conditions. There thus exists remarkable potential for newly-generated neurons in the senescent hippocampus to make important circuit- and behavioral-level contributions, which may serve as a target for future therapeutics.

Keywords

Senescence; neuroplasticity; memory; age-related cognitive decline; Alzheimer disease; dentate gyrus

Introduction

Normal age-related cognitive decline is a well-known and pervasive phenomenon [1]. Neuroplasticity, the ability of neural networks to adapt and remodel given experience, seems to dwindle with age, providing possible mechanistic insights into this decline. Accumulating evidence shows older neurons exhibiting slowing protein synthesis, decreased neurotrophin

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expression, and synapse loss [2-4]. Decreased neuroplasticity with aging can also be seen at the behavioral level, for instance as elderly persons develop compensatory strategies to counteract age-related decreases in executive and sensorimotor processing and flexibility [5]. Another layer of neuroplasticity, unique to a couple of discrete areas of the adult mammalian brain, is the addition of newly-generated neurons into existing circuits, a process known as neurogenesis. The hippocampus, a temporal lobe structure critical for the inherently dynamic processes of learning and memory, is one such area that exhibits ongoing hippocampal neurogenesis across the lifespan, although the extent to which this holds true in humans, especially as we age, has recently sparked debate again. No matter what conclusions will eventually be reached, over the past couple of decades, there has been an enormous number of studies revealing how new dentate granule cells are generated, integrate into the existing circuits and participate in regulating hippocampus-engaging behaviors. The electrophysiological- and circuit-level work has been based largely on data from rodents [6-9], while some work, especially pharmacological and behavioral, has been conducted in non-human primates [10, 11]. Importantly, how the generation and integration of new dentate granule cells occurs and potentially contributes to dysfunction under pathological conditions is becoming increasingly clear. In contrast, neurogenesis in the aging brain has scarcely been investigated. Given that memory loss is an important component of age-related cognitive decline, the mechanisms by which this faculty becomes compromised with age, whether hippocampal neurogenesis has any role to play, and possible strategies to combat such progression, are of great interest.

In this review, we briefly highlight the current knowledge regarding hippocampal neurogenesis in the aging brain, tying the basic biology gleaned largely from studies of rodents and non-human primates to the current evidence in humans.

Declining hippocampal neurogenesis with age: mechanisms and implications

Mammalian hippocampal neurogenesis peaks in the early postnatal period and declines rapidly thereafter, although it persists into adulthood. This knowledge dates back to the 1960s with the classic radiolabeling experiments of Altman and Das [12]. An implicit assumption that remained dormant in the field was that adult hippocampal neurogenesis was probably relevant for juvenile and young adult animals, but unlikely to be important for older animals. In the late 1990s, researchers interested in this question discovered that hippocampal neurogenesis indeed continues into old age in 26 month old rats, in which ~1000 proliferating cells could be detected per day, or roughly half that detected in 5-month-old younger adult rats [13]. Perhaps more relevant to humans, who are relatively much longer living than rodents, several studies have investigated the presence of hippocampal neurogenesis in aged non-human primates. Gould and colleagues were the first to demonstrate the presence of recently-proliferated hippocampal cells in adult macaque and rhesus monkeys (*Macaca fascicularis* and *Macaca mulatta*) [14]. They showed that macaques and rhesus monkeys injected with the thymidine analog BrdU displayed uptake of this analog in newly-born (TOAD-64+) hippocampal granule cells even up to age 23 and 12, respectively. Importantly, however, the number of newborn neurons dropped sharply after

young adulthood to low but still detectable levels in aged animals. These findings were replicated by an independent group, lending further support to the presence of aged adult neurogenesis in primates [15]. Furthermore, older adult (up to 7-year-old) marmoset monkeys (*Callithrix jacchus*) exhibited significantly fewer surviving 3-week-old BrdU-labeled adult-born hippocampal neurons as compared to their juvenile and young adult counterparts, whereas total number of mature (TuJ1+) neurons and (GFAP+) astrocytes remained comparable across life [16].

The mechanisms explaining this decay in rate of neurogenesis became a natural next question. An extensive line of investigation revealed that steroidal signaling likely plays a role in regulating the rate of hippocampal neurogenesis, and may partially explain declining rates in aged animals. For instance, performing adrenalectomy in aged rats, thereby removing the primary source of corticosteroid production, profoundly increases proliferation of stem cells and increases the number of TOAD-64+ immature neurons to levels comparable to those of juvenile rats, begging the question of whether there exists a quiescent pool of potentially activeable neural stem/progenitor cells (NSPCs), or perhaps a means of suppressing the death of progenitor cells, and/or a means whereby newly generated neurons could exhibit enhanced survival and integration [13]. More recent data has shown that under basal (i.e., adrenal gland-intact) conditions, last possibility is most likely, given that the fraction of dividing stem/progenitor cells stays roughly the same throughout life, although the level of neurogenesis decreases [17]. At the molecular level, low levels of cortisol increase proliferation but ultimately temper neurogenesis via mineralocorticoid receptor-mediated activation of the Notch/Hes and Hedgehog signaling pathway, while high concentrations of cortisol decrease both proliferation and neurogenesis via activation of both glucocorticoid and mineralocorticoid receptors leading to inhibited TGFβ-SMAD2/3 and Hedgehog signaling [18]. Moreover, high levels of glucocorticoids chronically activate NMDA receptor-dependent excitatory transmission, thus suppressing progenitor cell proliferation [19, 20]. This dose-dependent effect of corticosteroids on proliferation and neurogenesis may explain differences between levels of cell cycling in the hippocampus under basal versus chronic stress conditions. As aging is associated with elevations in markers of systemic inflammation and oxidative stress in humans [21, 22], aging may in and of itself be considered a form of a low level chronic stress state.

Given these demonstrated actions of glucocorticoids on hippocampal proliferation and neurogenesis, might this help explain the age-dependent decline in neurogenesis? As alluded to above, this mechanism is certainly not the whole story, however the hypothalamic-pituitary-adrenal (HPA) axis, which auto-regulates circadian fluctuations in glucocorticoid levels, increases its activity across the lifespan, with higher basal glucocorticoid levels exhibited by older individuals [23]. Furthermore, the expression of glucocorticoid and mineralocorticoid receptors on hippocampal NSPCs increases with age, perhaps leading to increased sensitivity of these cells to circulating hormones and lower thresholds for excitation-induced suppression of proliferation and neurogenesis [24].

Apart from neurohormonal regulation of aged hippocampal neurogenesis, decreased survival of newly-generated neurons is also a product of immune activity that varies across the lifespan. For instance, the hippocampi of aged (24-28-month-old) mice contain a higher

density of Iba1 (microglial marker) compared to those of young adult (2-month-old) mice, which is also reflected in a similar discrepancy in mRNA levels of the pro-inflammatory cytokine interleukin (IL)-1β [25]. More importantly, while neural stem/progenitor cell viability is not affected by high levels of IL-1β *in vitro*, trimethylation of the NeuroD promoter in these cells (required for differentiation into dentate granule cells [26]) is significantly increased by IL-1β exposure, suggesting a causative role of cytokine signaling in epigenetic regulation of progenitor cell fate determination. Increased hippocampal microglia also serve to clear the cellular debris from apoptotic cell bodies via phagocytosis, as microglia retain high phagocytic efficiency even in old age [21]. These data suggest that new hippocampal neuron generation and integration may be limited in senescence by microglia stalling progenitor cell differentiation, and that microglia may also be recruited in increasing numbers to clear the debris generated by more non-surviving newborn neurons at older ages.

The mechanisms that have been proposed to explain declining neurogenesis with age have been largely worked out in rodent models. By contrast, limited evidence comes from aged non-human primate data, likely due to a comparative lack of precise genetic and molecular tools that can be used for experimental manipulation, as well as the costs associated with research in aged non-human primates. What is known based on non-human primate literature comes predominantly from pharmacological and behavioral studies. For instance, Aizawa and colleagues found that learning performance on a hippocampus-dependent behavioral task correlates positively with the number of Ki67+ (proliferative) cells in the subgranular zone (SGZ) of the dentate gyrus of aged macaque monkeys [28]. Importantly, the anti-depressant effect of the selective serotonin reuptake inhibitor (SSRI) fluoxetine is dependent on hippocampal neurogenesis in adult bonnet monkeys [29]. While hippocampal volume was found to be larger in fluoxetine-treated adult (10-12-year-old) baboons compared to vehicle-treated, aged-matched controls, surprisingly, fluoxetine treatment resulted in *fewer* total immature neurons (DCX+) [30], suggesting that the neurogenic response to serotonergic manipulation in the hippocampus may differ across species [31]. Yet to our knowledge, no studies directly demonstrating pharmacological manipulation of proliferation or neurogenesis in aged non-human primates or humans exist. At present, our best data comes from aged (~400-day-old) mice treated chronically with fluoxetine, which exhibit no significant changes in hippocampal cell proliferation or 4-week survival [32]. By contrast, younger adult (~100-day-old) mice exhibit a sharp increase in survival of 4-week-old BrdU-labeled cells, although proliferation is unaffected by fluoxetine treatment, as in the aged cohort. Thus, given these inconsistencies between aged rodent and non-human primate findings regarding synaptic regulation of neurogenesis, this area remains ripe for future research.

So far, the phenomenon of decreasing hippocampal neurogenesis and possible explanations have been explored, however, are there functional consequences of such diminishing numbers of new hippocampal neurons with age? Here, as is often the case in studies of animal behavior, the evidence is mixed. For instance, some studies have found significant correlations between rates of neurogenesis among aged rats and spatial/contextual memory performance [33, 34], while others have failed to detect such a link [35, 36]. In humans, while current technology and ethical considerations limit our ability to manipulate

neurogenesis to measure behavioral outcomes, correlational anatomical studies have found significant positive associations between hippocampal volume and hippocampus-dependent memory expression in aged humans, as well as inverse correlations between circulating glucocorticoid levels and either hippocampal volume or memory expression [37-39]. Of course, it bears mentioning that human hippocampal volume is a poor surrogate for neurogenesis, and that a direct link between the two has yet to be firmly established.

On the other hand, targeted experimental manipulation of neurogenesis by others and us have clearly shown important, time-sensitive roles of newborn hippocampal neurons in memory expression in young adult rodents [40-43]. Yet, limited evidence exists to confirm these findings in older animals, possibly due to technical limitations or feasibility in direct genetic manipulation or virus-mediated gene delivery in aged animals.

Stimulating cell cycling and enhanced neuronal survival/integration in old age

While baseline levels of hippocampal neurogenesis in the aged animal may or may not be important for day-to-day hippocampal functioning, it still seems worthwhile to know whether enhancing neurogenesis in old age (if possible) could restore any age-related memory impairments. In fact, many groups have begun to delve into these questions, with surprising results.

In the early 2000s, the latent potential of the aged dentate gyrus to dramatically upregulate production of new neurons even in senescence was discovered. Aged mice given enriched environmental experiences, well-known to potently stimulate neurogenesis in young adult mice, exhibited a marked increase in neurogenesis, with levels comparable to those of juveniles [44, 45]. After initial provocative studies like this, follow-up investigations explored whether other interventions known to stimulate neurogenesis in youth could similarly be employed with good effect in aged animals. Voluntary, physical aerobic exercise was soon shown by the same group to yield a similar effect, restoring neurogenesis in aged mice to about half the level of that seen in mice 15 months younger [46]. Pharmacological manipulation with the selective serotonin reuptake inhibitor (SSRI) fluoxetine, known to stimulate neurogenesis in young adult mice, similarly increased neurogenesis in aged mice and rats [47-50]. Artificially increasing the blood supply to the hippocampus through enhanced angiogenesis also potently stimulates hippocampal neurogenesis in aged mice [51]. Finally, our laboratory has also noted that signaling through bioactive lipids can substantially upregulate neurogenesis in aged mice (unpublished observations). How could such marked increases in neurogenesis in the aged brain, which exhibits such low basal levels, be possible?

Mechanistically, there are several stages in the developmental sequence of new neuron generation that are potentially susceptible to manipulation. The first would involve theoretical changes in proliferative potential of neural progenitors, for which there is limited evidence. While the NSPC pool declines across the lifespan, individual stem cells are no less likely to cease dividing with age [17, 52]. These stem cells can divide asymmetrically to produce astrocytes or transit amplifying cells (which ultimately give rise to new neurons),

but retain their “stemness” property of self-renewal [17]. In addition, neurogenesis can be influenced by promoting or suppressing elimination of advanced progenitors [17]. While asymmetric division of NSPCs is the norm, there are conditions unrelated to aging that involve stem cells depletion via a separate mechanism involving symmetric division and consequent decreased neurogenesis. For instance, in the context of kainate-induced seizure activity, stem cells divide symmetrically to give rise to terminally differentiated reactive astrocytes [53].

Which stage may be susceptible to interventions that promote neurogenesis in the aged hippocampus? Enhanced neurogenesis in senescence may be achieved through reactivation of quiescent NSPCs. Lugert and colleagues showed that canonical Notch signaling can be upregulated in aged hippocampal quiescent Hes5+ NSPCs, leading to re-entry into the cell cycle and ultimately self-renewing as well as giving rise to multipotent progenitors capable of differentiating into neurons and astrocytes [54]. It is worth noting, however, that the stem and progenitor cells in this study may be limited to the Notch-reactive subpopulation of stem cells or RGL cells, as Hes5 is a Notch-regulated gene. Corroborating this evidence, upregulating neurogenesis in aged animals via vascular endothelial growth factor (VEGF)-mediated induction of angiogenesis can increase the number of BrdU-labeled RGL cells and induce morphological changes in these cells reminiscent of their juvenile predecessor cells [51]. Yet, this study did not actually demonstrate that it was the quiescent NSPCs which had been stimulated to reenter the cell cycle. Thus, it appears as though despite ever-diminishing numbers of surviving newborn neurons as animals age, there remains the potential for generation of a substantial number of new neurons that can integrate into the hippocampal circuit, although the subpopulations of stem/progenitor cells that may be susceptible to various interventions remains to be completely elucidated.

Are these newly-generated neurons in aged hippocampi the same as those of their younger counterparts in terms of properties and functions? While the answer to the latter question remains to be determined, efforts have been underway to understand the physiology of newborn neurons in the aged hippocampus. Trinchero and colleagues recently discovered several unique qualities of these cells, which again supports the notion of a pool of cells ready to rapidly integrate into the pre-existing circuit given the right cue [55]. Interestingly, at baseline, these young neurons in old hippocampi which as mentioned are few and far between, tend to be developmentally immature and scantly connected to the preexisting circuit for a prolonged period of time as compared to young neurons of the same age in young animals. However, in the context of a neurogenesis-promoting stimulus, in this case aerobic exercise, environmental enrichment, or neurotrophin exposure, the new neurons in the aged hippocampi rapidly elaborate their dendritic trees as well as maturing electrophysiologically, facilitating functional integration. Thus, there remains hope that even in the aged brain, new neurons not only can be produced, but also that they can still indeed hook into the circuit and possibly contribute to ongoing network activity and behavior. The Table summarizes key changes in hippocampal neurogenesis across the adult lifespan.

Hippocampal neurogenesis in aged adult humans: area for further study

It is natural to wonder, given all of the study of neurogenesis in aged experimental animals, whether adult neurogenesis persists into adulthood in humans. Newly-divided neurons have been seen in the hippocampi of 58- to 72-year-old terminally ill cancer patients treated with the thymidine analog bromo-deoxy-uridine in a classic study of neurogenesis in humans [56]. Yet, recent evidence has brought this firmly-held belief into question, as Sorrells and colleagues failed to detect DCX/PCA-NCAM double-labeled subpopulation of cells after childhood in post-mortem hippocampi from humans who died mostly from non-CNS-related causes, as well as from hippocampi resected from patients with epilepsy [57]. In the case of the “normal” subjects, however, one must question whether the physiological stressors that led to the cause of death may have suppressed neurogenesis that may have otherwise been observed in healthy individuals whose brains could not be examined due to the post-mortem nature of this study. With regard to the subjects with epilepsy, given that seizure activity is known to promote NSPC proliferation, the tissue samples taken from patients with epilepsy would be expected to exhibit this property (and indeed proliferative markers Ki67 and Mcm2 have been reported in the granule cell layer of humans aged 17-85 with epilepsy [58]), however it is also the case that in chronic epilepsy, neurogenesis is aberrant and stem cells may become depleted over time, potentially obscuring the measure of neurogenesis in this condition [53, 59, 60]. In any case, these findings have been difficult to reconcile with other lines of evidence.

For instance, quiescent radial glia-like (RGL) NSPCs (GFAP+, Sox2+, BLBP+, Nestin+ cells) as well as a small number of immature neurons (PSA-NCAM+) have indeed been detected in human subjects aged 20 to 80 [61]. Likewise, mRNA of Ki67 and DCX have been detected across the lifespan from ages 18 to 88 in human subjects, albeit at decreasing levels with age [62]. New evidence suggests that the issue of human newborn hippocampal neuron detection may be simply related to the fixation technique implemented [63]. Moreno-Jimenez and colleagues discovered that time in fixative and type of fixative used for human hippocampal samples critically affected adequacy of visualization of DCX and PSA-NCAM signals. They demonstrated that under optimized conditions, thousands of DCX+ cells could be detected in the aged adult human DG, and further, that in patients with Alzheimer disease (AD), DCX+ newborn neurons were fewer in number and also exhibited delayed maturation (assessed via emergence of Prox1 expression, indicating dentate granule cell fate commitment, as well as other markers of maturation).

Clearly, there remains more work to be done with regard to the question of human neurogenesis in adulthood and senescence. The existing limited data highlight the main limitation of this work, which is that it relies heavily on expression of mRNA and protein markers presumed to represent neural stem cells and newborn neurons in humans. Independent and more direct methods of detecting neurogenesis (for example, actually observing cell division and synaptic integration in slice culture preparations) will likely be needed to solve this conundrum. Furthermore, it would be interesting to see whether aged humans who had exposure to neurogenic stimuli would exhibit as robust a response as has been seen repeatedly in animal studies.

A recent attempt to reconcile the short- and long-lived experimental animal and human data emphasized possible differences in the neurodevelopmental sequence of maturation across species [64]. More specifically, based on the existing literature Snyder pointed out that the peak and decay in neurogenesis varies considerably from humans to non-human primates to rodents, relative to birth and onset of sexual maturity, with human neurogenesis peaking earliest and rodent neurogenesis peaking latest. Therefore, in interpreting the results of any study of hippocampal neurogenesis, it is important not only to consider the *biological* age of the animals used in the experiments, but also their *developmental* age with respect to the progression of neurogenesis over time and relative to humans. It is important to bear in mind, however, that the total number of newborn neurons generated and integrated at a given time may not necessarily reflect these cells' overall contribution to the hippocampal trisynaptic circuit, as even a small number of newborn granule cells can substantially impact both circuit activity and behavior [41, 65, 66]. Therefore, our fixation on absolute numbers should be tempered by an appreciation for the sizeable impact of even a small number of adult-generated dentate granule neurons.

Conclusions

Recently, there has been a resurgence of research into the regenerative capacity of the hippocampus in old age, and for good reason. With an ever-aging population and an estimated prevalence of Alzheimer disease of 5.7 million people in the United States alone, the impetus for more targeted treatments for age-related cognitive disorders is greater now than ever [67]. While no therapies specifically targeting hippocampal neurogenesis have been proven to slow or reverse age-related cognitive or memory function (and indeed, there remains debate regarding the actual existence and possible relevance of human adult hippocampal neurogenesis), recent findings support the idea that the hippocampus remains remarkably plastic even in old age. The next steps include better understanding of the properties and functionality of young neurons produced by aged hippocampi, and determining whether these cells can be manipulated and harnessed to facilitate cognitive functioning in normal as well as pathological aging. Put simply, in the coming decade, we need to learn more about hippocampal neurogenesis, circuit integration of new neurons, and the function of this process spanning from the prenatal period to the end of life.

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Table.

Qualitative comparison of hippocampal neurogenesis in the young and aged adult animal.

	Young adult hippocampal neurogenesis	**Older adult hippocampal neurogenesis**
Stem cell population	Many quiescent and some active RGL cells dividing asymmetrically to self-renew or give rise to new neurons or astrocytes [53, 54, 68]	Loss of number of RGL cells (“deforestation”) without change in ratio of quiescent and active populations (sharper decrease in RGL cell number in non-human primates vs. rodents but similar trend in proliferative potential); increasing symmetric division to give rise to astrocytes [17, 27, 52, 53, 69].
Morphological development and integration of newborn neurons	Relatively rapid maturation and integration (4-8 weeks) [41, 70]	Relatively slow maturation and integration (10-14 weeks) [55]
Response to neurogenic stimulus	Modest increase in neurogenesis vs. baseline (generally up to ~1.5-2-fold increase); relatively fast maturation and functional integration, accelerated by neurogenic stimulus. Variable response to selective serotonin-reuptake inhibitors across species [30, 31, 45, 46, 71, 72]	Marked increase in production of IPCs and new neurons vs. baseline (up to ~5-fold increase); slow functional maturation at baseline, rapid integration with stimulus. Variable response to selective serotonin-reuptake inhibitors across species [30, 32, 44, 46, 51,55]

RGL: Radial glia-like

IPC: Intermediate progenitor cell