Trends in Neurosciences

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Feature Review

Recalibrating the Relevance of Adult Neurogenesis

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Conflicting reports about whether adult hippocampal neurogenesis occurs in humans raise questions about its significance for human health and the relevance of animal models. Drawing upon published data, I review species' neurogenesis rates across the lifespan and propose that accelerated neurodevelopmental timing is consistent with lower rates of neurogenesis in adult primates and humans. Nonetheless, protracted neurogenesis may produce populations of neurons that retain plastic properties for long intervals, and have distinct functions depending on when in the lifespan they were born. With some conceptual recalibration we may therefore be able to reconcile seemingly disparate findings and continue to ask how adult neurogenesis, as studied in animals, is relevant for human health.

Highlights

Animal work has revealed that immature neurons born in the adult dentate gyrus have key cellular and behavioral functions.

Recent reports are conflicted about whether adult neurogenesis occurs in humans.

Discrepancies could arise from species differences in neurodevelopmental timing and differences in subject ages.

Regardless of its extent, postnatally, an extended period of neurogenesis may produce a heterogeneous population of dentate gyrus neurons, due to prolonged cellular maturation and differences in the stage of the lifespan when neurons are born.

These developments warrant a recalibration of when and how dentate gyrus neurogenesis contributes to cognition and mental health in humans.

The Continuous Controversy of Adult Neurogenesis

While broadly recognized today, the prospect of adult neurogenesis was essentially nonexistent until the 1960s when Joseph Altman reported that neurons continue to be produced throughout adulthood [1,2]. Despite its implications (or perhaps because of them), further research on adult neurogenesis stalled until the 1990s when advances in immunohistochemistry and microscopy enabled the unambiguous identification of birthdated neurons [3]. Since then, there have been debates about methodological accuracy, the brain regions that harbor adult neurogenesis, and the species that possess it [4–8], but the general consensus for the past decade has been that neurons are added, in adulthood, to at least one brain region in humans and most mammals: the dentate gyrus (DG) subregion of the hippocampus [9–12].

A recent high profile report, arguing that hippocampal neurogenesis ends in childhood in humans [13], has reignited the controversy [14–20]. However, a closer look reveals that this is not the only study reporting that features of neurogenesis, whether stem cells, mitotic cells, or immature neurons, decline to low or absent levels by childhood [21–25]. While methodological factors may contribute to the discrepancies between studies that do and do not observe signs of human adult neurogenesis [15], uncertainty may also stem from more general differences in study design and interpretation [26]. For example, human studies that have included fetal and infant subjects often conclude that neurogenesis ends in childhood, but note the occasional sign of neurogenesis in older subjects [13,23–25]. Conversely, studies that have solely examined adults report ongoing DG neurogenesis, but at low rates [11,12]. Now that a reasonable amount of quantitative data exists for both humans and animals, I attempt here to objectively address the issue by comparing lifelong patterns of DG neurogenesis across rodents, nonhuman primates, and humans. It is worth noting that adult neurogenesis in the subventricular zone–olfactory bulb is well characterized [27], and new neurons have also been described in the adult mammalian neocortex [28] and striatum [29], among other regions [8]. However, since too few quantitative datasets exist for these regions for a comprehensive comparison, here I will focus on the DG.

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Critical Periods and Functional Properties of Adult-Born Neurons

Before continuing, it is important to clarify exactly why we care about adult hippocampal neurogenesis. A comprehensive review of its behavioral functions is beyond the scope of this article, but suffice it to say that animal work has demonstrated that adult neurogenesis is causally involved in many of the functions of the hippocampus. New neurons promote flexible learning and adaptive behavioral and endocrine responses to cognitive and emotional challenges [30–32]. The potential relevance for mental health is also substantial since neurogenesis may be involved in many disorders that are known to impact the hippocampus including depression, anxiety, schizophrenia, addiction, epilepsy, age-related memory loss, and dementia [33,34].

Behavioral functions of hippocampal neurogenesis have been identified almost exclusively from rodent studies. One can also turn to cellular properties that speak to function, some of which I will compare across human and animal models. Foundational studies in rodents, particularly mice, have revealed that new neurons progress through discrete stages of maturation into hippocampal circuits [35,36] (Figure 1). Particularly relevant for theories of memory, and hearkening back to classic studies of developing systems, adult-born neurons have a critical period for plasticity and excitability during their immature stages. From 2–6 weeks of age they have a lower threshold for long-term potentiation (LTP) of their cortical inputs, due to the presence of T-type Ca^{2+} channels, NR2B-containing NMDA receptors and reduced

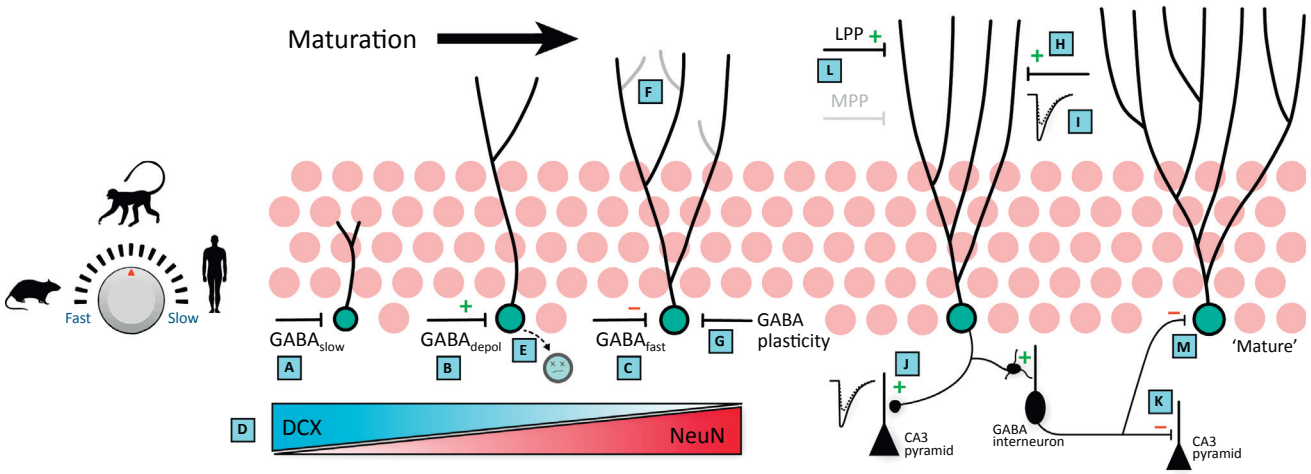

Figure 1. Neuronal Maturation and Critical Period Properties. Many key maturational steps occur over the first weeks of neuronal life, when adult-born neurons possess unique properties during a critical period. As identified in rodents, during the first few weeks (A) adult-born neurons first receive slow GABAergic signals [36], then (B) depolarizing and trophic GABAergic inputs [44,151], and finally (C) fast GABAergic and glutamatergic synaptic inputs [36]. Over this interval they (D) lose expression of the immature neuronal marker, DCX, and gain higher levels of NeuN expression [152]. Experience modulates (E) neuronal survival [153], (F) dendritic remodeling [154], and (G) alters long-range GABAergic innervation [49]. At ~4 weeks of age, new neurons (H) are more efficiently recruited by afferent inputs [155], (I) they have enhanced afferent [40] and (J) efferent [41] synaptic plasticity, and (K) they drive feed-forward inhibition [156]. Immature adult-born neurons also (L) receive inputs primarily from the lateral entorhinal cortex [139,140], (M) promote [157] or differentially contribute [43] to feedback/lateral inhibition in the DG, have different functions in memory [158] and have distinct receptive fields during behavior [53] (not shown), although it remains unclear whether these properties are lost as cells mature. It is generally believed that as they mature, adult-born neurons exit these critical periods and become functionally similar to the general population. However, there is evidence that some unique properties persist beyond the traditional critical period, and depend on when in the lifespan a dentate granule neuron was born (see Figure 4). Moreover, rodent studies have revealed that the timeframe of maturation is slowed dramatically with age [98,159]. The dial on the left highlights the fact that, while little is known about maturation rates in other species, studies of adult-born neurons in primates and longer-lived mammals [160], and studies of DG growth in humans [111,161], suggest the process is slower. In this way, later-born neurons might provide a substantial source of critical period plasticity for years after their birthdate. Abbrevations: DG, dentate gyrus; LPP, lateral perforant path; MPP, medial perforant path.

GABAergic inhibition [37–40]. Adult-born neurons also display enhanced LTP at their efferent synapses onto CA3 pyramidal neurons at 4 weeks of age, relative to 2 and 8 weeks [41]. Differential excitation–inhibition properties also cause immature neurons to uniquely respond to, filter, and integrate synaptic inputs [42–45]. Structurally, learning and environmental enrichment alter the survival and connectivity of adult-born neurons during defined windows of immaturity [46–50]. These unique properties are likely to endow adult-born neurons with distinct roles in sensory processing and memory [51–53]. Indeed, behavioral changes arise within weeks after arresting neurogenesis, indicating that these immature neurons are functionally important [54–56]. The transient nature of these critical periods, along with evidence that adult-born neurons become broadly comparable to developmentally born neurons [57,58], suggests that neurogenesis ultimately results in a homogeneous population of DG neurons. Some have even proposed that, after a transient period of functional potency, DG neurons become silent with age [59,60]. According to this perspective, an early decline in human neurogenesis could imply that there would be no meaningful neurons remaining in adulthood. After comparing neurogenesis rates across species, I therefore review emerging evidence that questions the exclusive and privileged role of immature DG neurons and suggests that some important functional properties are retained beyond the traditional critical window.

How Does Dentate Neurogenesis in Humans Align with Animals?

A number of considerations complicate the comparison of neurogenesis across species: neurogenesis declines with age, subject ages vary across studies, and neurodevelopmental timing differs between species. Accordingly, an objective comparison of neurogenesis levels across the full lifespan may help elucidate differences and commonalities between species. To this end, Figure 2 (Key Figure) displays neurogenesis rates from published studies of mice, rats, primates, and humans, plotted alongside each other (see the supplemental information online for details).

The general pattern of neurogenesis is similar across all species: early in life, neurogenesis rapidly rises and falls, and then remains at lower levels for most of the lifespan. However, there are notable species differences in the timing of neurogenesis, particularly with respect to birth. In humans, neurogenesis peaks in the first half of gestation and the DG is mostly formed by birth, consistent with qualitative reports [61]. In rodents, neurogenesis peaks later, around the time of birth, and continues at moderate to high levels during the early postnatal period. The picture in rhesus monkeys is intermediate, with ~60% of neurons born prenatally and ~25% in the first three postnatal months [62] (in marmosets, a similar pre- vs postnatal pattern is observed [63]). The timing of DG neurogenesis is therefore consistent with the broader comparative pattern of neurodevelopment, where humans and nonhuman primates are born with a mature nervous system (at least in terms of cell production) compared to that in rodents [64,65]. Thus, defining birth as T_0 can be misleading and gives the appearance that neurogenesis is conspicuously low in primates and humans compared to rodents (Figure 2B; y axis still scaled to peak lifetime rates). In contrast, when aligning T_0 to the date of conception (Figure 2A), the postnatal differences seem reasonable given the amount of prenatal neurogenesis that occurs in primates and humans. Indeed, a comparative analysis found that neurogenesis rates decline with absolute age and are not proportionally extended in longer-lived mammals [66]. Also, a recent modeling study has suggested that human and animal DG neurogenesis rates are generally consistent with one another once species differences in neurodevelopmental timing are accounted for [19].

DG neurogenesis is often labeled as developmental or adult but these distinctions are typically ill defined (discussed in [67]). Since neurogenesis is continuous, it is reasonable to consider it as a

Key Figure

Comparison of Neurogenesis across the Lifespan

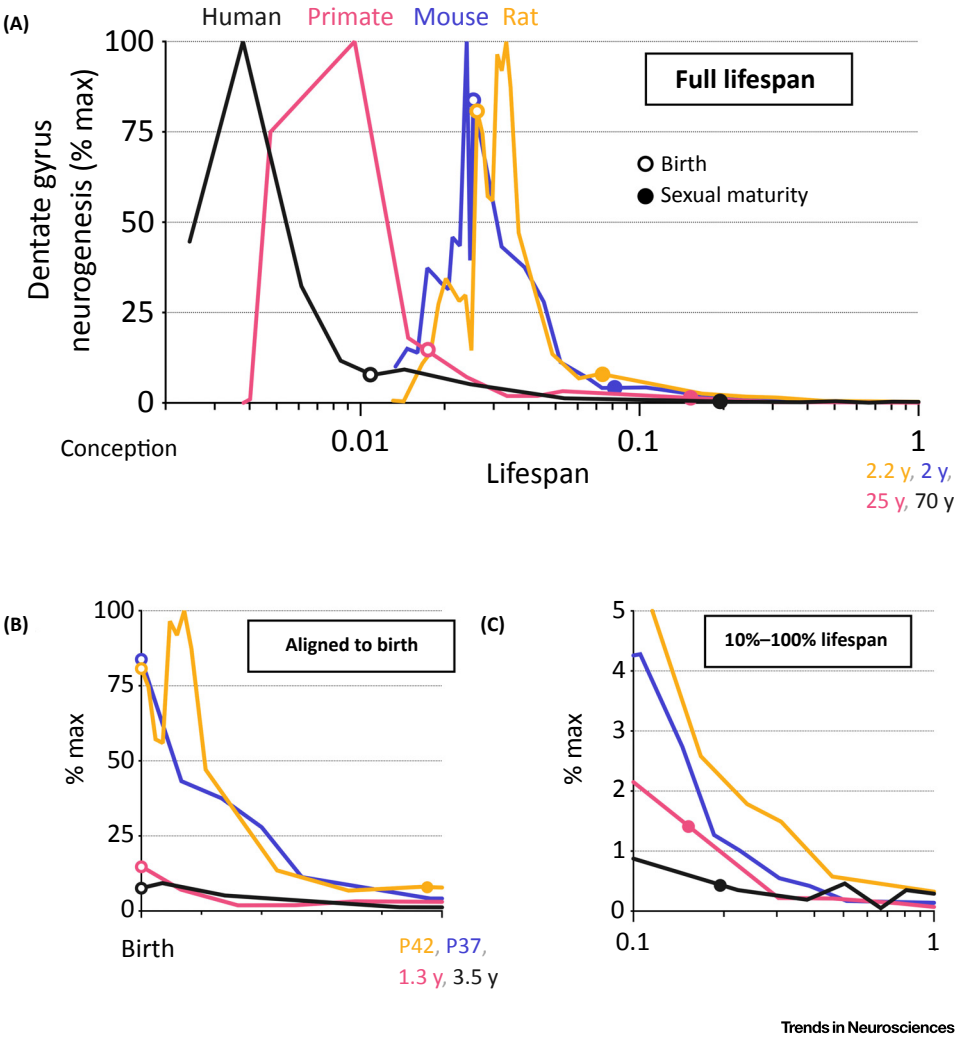

Figure 2. (A) To objectively compare neurogenesis rates, published data of mitotic markers (^{3}H-Thy, BrdU, and Ki67) were used (and extracted from graphs with Plot Digitizer where necessary). Ranges of overlapping ages allowed different studies to be normalized to one another, with peak neurogenesis set at 100%. For mice, studies by Angevine [162], Ben Abdallah *et al*. [163], Mathews *et al*. [164], and Kronenberg *et al*. [165] span the full age range, from the onset of DG neurogenesis at E10 to near the end of the lifespan, at 2 postnatal years. For rats, studies by Schlessinger *et al*. [119], Altman and Das [166], and Kuhn *et al*. [167] span embryonic day 11 to 2.25 postnatal years. For primates (rhesus monkeys), studies by Jabes *et al*. [62] and Ngwenya *et al*. [75] cover the end of the embryonic period (E140) through the majority of postnatal life (up to 25.5 years). There are no quantitative studies (to our knowledge) of prenatal DG development but Rakic and Nowakowski [120] describe a highly neurogenic period from E45 to P32. Since cells that span the width of the granule cell layer are generated from E60 to E120, E90 was designated as an approximate peak of primate DG neurogenesis. Timepoints before (E45) and after (E140) were adjusted to produce a curve where 40% of DG neurons are generated postnatally in 7-year-old monkeys [78]. For humans, studies by Yang *et al*. [168], Sorrells *et al*. [13], Seress *et al*. [23], and Dennis *et al*. [24] have quantified Ki67 from gestational week 9 to 59 years. Since rates of decline varied, data points were averaged across studies as follows. First, counts were converted to cells/mm^3 based on the section thickness used in the study. Up to birth,

(Figure legend continued on the bottom of the next page.)

unitary, but protracted, phenomenon. The pattern of early DG neurogenesis is therefore likely to impact neurogenesis later in life, potentially contributing to species differences. For example, accelerated DG development in humans may lead to lower rates of neurogenesis in childhood and adulthood if DG precursor cells undergo a finite number of divisions [68–70]. This is suggested by Figure 2C, where postnatal neurogenesis rates are lower in humans until about halfway through life, when in rodents the rates decline to comparable levels.

In contrast to the dynamic changes early in life, neurogenesis rates are more stable in the second half of the lifespan and remain at 0.1–0.5% of maximum levels across all species (Figure 2C). Middle- and old-aged rodents typically have hundreds of cells that are born per day [71–73], and rhesus macaques have thousands (mid age) to hundreds (old age) of labeled cells [74,75]. Assuming ~600 000 DG granule neurons in mice [76], ~2 400 000 in rats [77], and ~7 000 000 in rhesus macaques [75,78], this translates to less than 0.1% of DG cells in middle age and less than 0.01% in old age. This could be seen as reasonably on par with the proportion of DCX^+ cells in adult humans (~0.005%, [79]) and the rate of daily turnover estimated by ^{14}C dating (0.004%, [10]). Commonly-used histological methods that only detect new cells generated in a snapshot of time will therefore reveal only one new cell for every 10 000 + DG neurons, which amounts to few or no cells per brain section. This may be high enough to detect in controlled animal studies but too low to reliably detect in human samples.

The data in Figure 2 provide a semiquantitative starting point for reconciling DG neurogenesis in humans and animals. Differences in developmental timing may explain why rodents have greater neurogenesis than primates and humans, particularly in early postnatal life. While the data cannot definitively address whether neurogenesis falls to zero in one species and not another, it suggests that middle- to old-aged humans and animals are not so different from one another in that few neurons (in proportion to the total number of DG neurons) are added, on a daily basis, for much of the lifespan (see also [80]).

Age-Related Sampling Biases in Neurogenesis Studies

Why might negative human reports generate concern when new neurons are in fact fairly rare in animals in later stages of the lifespan? One possibility is that the overwhelming focus on young animals in neuroscience research [81] inflates the perceived magnitude of adult neurogenesis. To explore this possibility, we examined subject ages in published studies of adult DG neurogenesis and found that neurogenesis tends to be examined at young ages in rodents, when neurogenesis levels are high (median age of 90 days, 12% lifespan; Figure 3). In contrast, the ages of human subjects span the full lifespan, and the majority are beyond the age when neurogenesis has plateaued at low levels (median age 44 years; 63% lifespan). Rodent studies

time points and cell counts were grouped and averaged across studies if they fell within 3 weeks of the mean age of the group. With age, the window expanded such that for the first year of life subject ages were grouped if within 1 month of one another. Subjects aged 2–9 years were pooled and all other time points reflected averages for respective decades of life. To be consistent with the animal data, which covered the entire lifespan, a data point was added for humans at 70 years [average human lifespan, World Health Organization; calculated by averaging the three prior data points (since the curve was asymptotic)]. The time scale on the x axis was normalized to postconception age (which approximates the species lifespan – mice: 2 years, rats: 2.25 years, macaques: 25.5 years, humans: 70 years). Ages of birth and sexual maturity are indicated by the circles that are embedded in the curves. They are merely meant to highlight, approximately, developmental milestones, and are not data points with regards to neurogenesis. For sexual maturity ages, the following estimates were used (postnatally): mice: 42 days, rats: 40 days, rhesus monkeys: 3.5 years, humans: 13 years. Data, calculations, and detailed discussion of methodology are available as supplemental material. (B) Aligning the early postnatal period to time of birth gives the impression that neurogenesis is greater in rodents than in humans and non-human primates. Graph shows 5% of lifespan. (C) Enlargement of 10–100% lifespan suggests that neurogenesis rates can be seen as broadly comparable across species later in life. Abbreviations: DG, dentate gyrus.

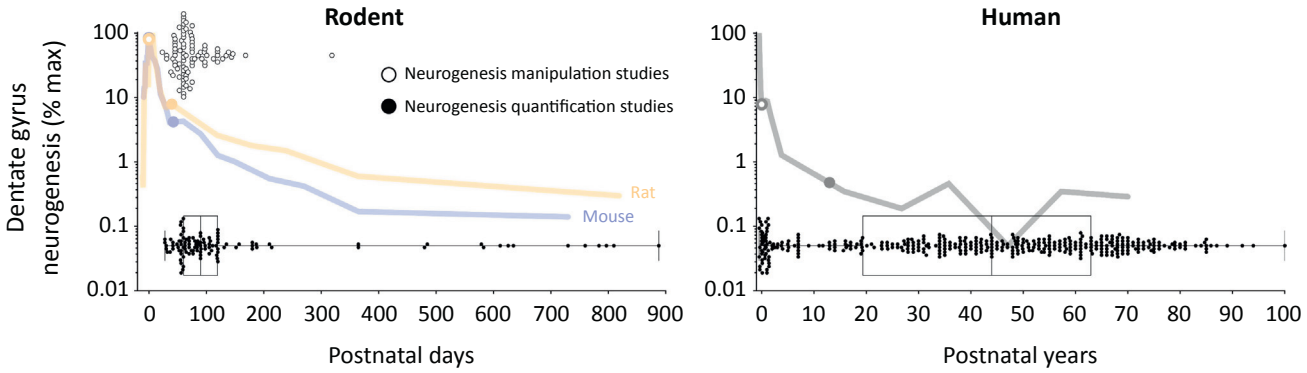

Figure 3. Subject Ages Differ in Rodent and Human Studies of Adult DG Neurogenesis. Subject ages in DG neurogenesis studies (horizontal scatterplots) are plotted alongside lifetime neurogenesis curves. Subject-age data points do not have y-axis values, but are overlaid on neurogenesis curves to facilitate comparison of the ages when subjects are sampled with the amount of neurogenesis at those ages. Filled symbols indicate subject ages when proliferation markers have been used to quantify adult neurogenesis; open symbols (rodents only) indicate subject ages when neurogenesis was manipulated in studies of behavioral function; boxes and whiskers indicate quartiles. In rodents, 75% of studies quantified neurogenesis rates at ≤4 months of age. At this age, the animals are considered young adults or adolescents; they only recently have reached sexual maturity and neurogenesis has not yet substantially declined. By contrast, in humans, 75% of subjects are beyond 19 years of age, when neurogenesis rates have largely plateaued at low levels. Neurogenesis quantification: rodent studies were identified in Pubmed using the search terms 'dentate gyrus' and 'neurogenesis', sorted according to date, and over 100 studies were randomly sampled with the exception that efforts were made to relatively evenly sample the period of 1994 to 2018. Animal age was defined as the age when cell birth was assessed (time of BrdU injection, or age of euthanasia for Ki67). If multiple BrdU injections were given, the average age was used. If multiple ages were examined, each age was included as a data point. Neurogenesis manipulation: rodent manipulation–behavior studies were identified by including additional search terms such as 'irradiation', 'tk', 'tmz', 'mam', 'arac', 'tamoxifen', 'chemogenetics', and 'optogenetics', in order to obtain a complete list of studies. Subject age was defined as the earliest age when neurogenesis manipulation began. Mice and rats are pooled for the rodent subject age datasets. For humans, the individual ages of 375 subjects from 14 studies are shown. Human studies were excluded if they did not provide individual subject ages and rodent studies were excluded if they did not define animal age. Since the intention was to compare rodent and human studies of adult neurogenesis, studies were excluded if they focused entirely on the prenatal or early postnatal period. A list of studies and ages is provided as supplemental material. Open and closed symbols that are embedded in the lifetime neurogenesis curves indicate birth and sexual maturity, respectively, as in Figure 1. Abbreviations: DG, dentate gyrus.

that have manipulated neurogenesis do so at even younger ages (median 60 days). Thus, neurogenesis is often studied soon after rodents reach sexual maturity (~P40), which is routinely used as a rough approximation of an adult-like stage of development. However, compared to humans, not only does neurogenesis peak later in rodents but sexual maturity occurs earlier (Figure 2A). Therefore, once ages and developmental differences are accounted for, it is not surprising that young adult-like rodents have greater neurogenesis rates than the middle-aged humans that comprise most studies.

Recalibrating According to Neurodevelopmental Timing

The data indicate that DG neurogenesis declines early in humans, raising the question of how it might be relevant for health. Possibly, low rates may have substantial cumulative effects as has been estimated for rats [82] and demonstrated in mice [83]. Spalding *et al*. estimated that only 0.004% of neurons are added each day in adult humans [10]. While this would appear negligible under the microscope (1 cell in 25 000), it translates to ~15% over a decade; a sizable fraction that could reasonably be expected to offset hippocampus-based mental health disorders.

Alternatively, if human neurogenesis ends in childhood, or if rates are too low to produce a meaningfully-sized population of highly-plastic neurons, it becomes important to recalibrate predictions about when in the lifespan DG neurogenesis is most relevant. Indeed, the high rates of neurogenesis in early postnatal mice may be relevant for understanding infantile amnesia [84]. Adult neurogenesis, as commonly studied in (young) animals, may be a more accurate model of childhood neurogenesis in humans, and may make less of a contribution to

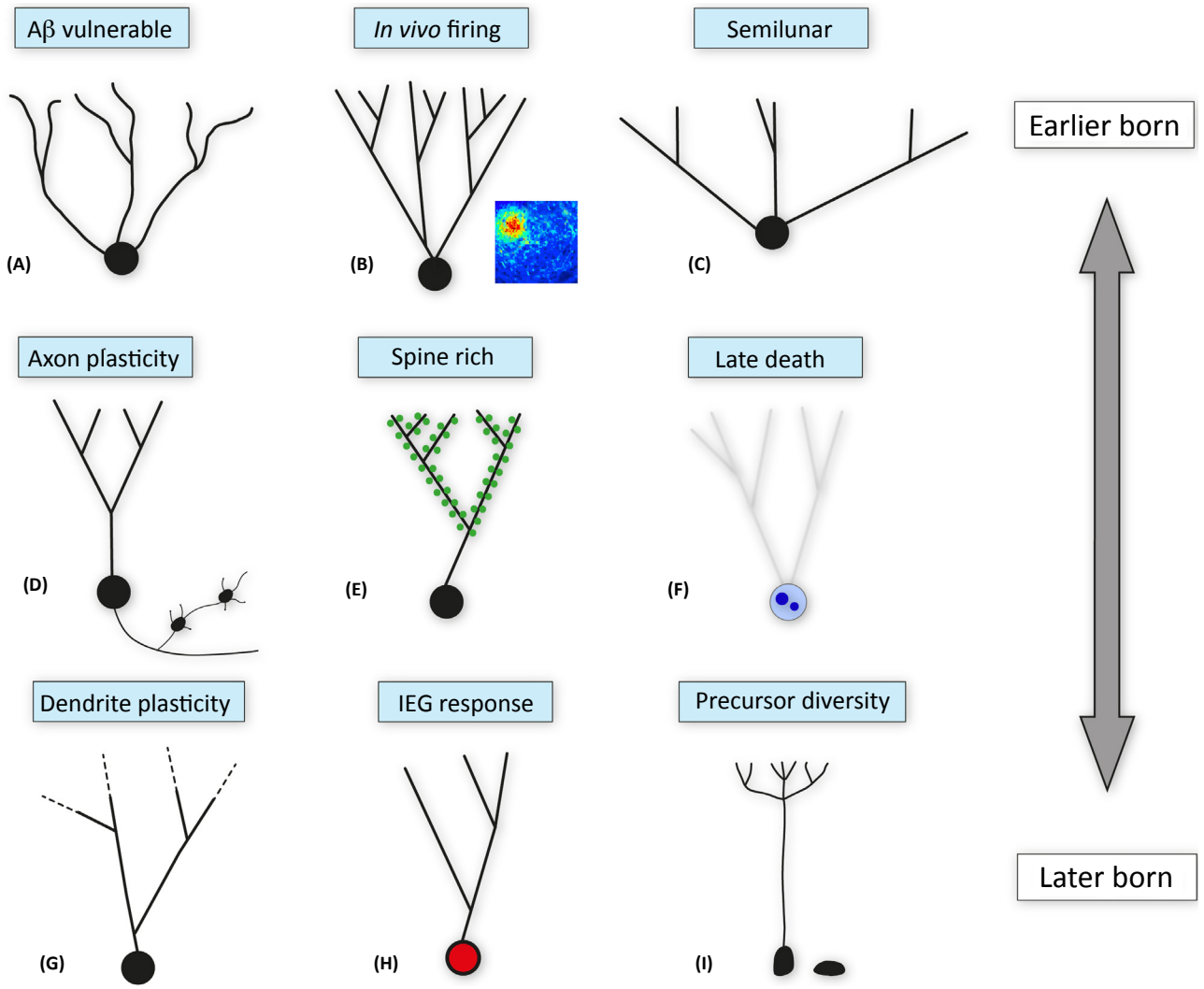

Figure 4. Ontogeny-Based Cellular Heterogeneity. DG neurons born at different stages of the lifespan acquire distinct properties, many of which persist throughout the lifespan of the cell. (A) Early-born, superficially-located neurons undergo atrophy in a mouse model of Alzheimer's disease [149]. (B) Mature-appearing, highly branched neurons are more likely to fire during spatial navigation [129]. (C) Semilunar granule neurons are born on ~E14 in mice [126,127]. (D) A subset of DG neurons have elaborate mossy fiber extensions [136] and (E) higher than usual spine density [108,109,135], although the age of these cells and their ontogenetic origins, if any, remain to be determined. (F) Neurons born in early postnatal rat development die at old (neuronal) ages [133,134]. (G) Old adult-born neurons display experience-dependent plasticity [100] and (H) unique patterns of IEG expression compared to early-born neurons [130,169] and depending on when in adulthood they were born [131]. (I) Heterogeneity in the DG precursor cell population may also contribute to neuronal diversity [170–172]. Abbreviations: DG, dentate gyrus; IEG, immediate-early gene.

hippocampal function and disorders later in life. As indicated in Figure 3, few have tested this hypothesis. However, blocking neurogenesis in 1-month-old mice has greater behavioral effects than in 3–4-month-old mice [85]. Additionally, one study found that new neuron functions in object recognition were absent in young irradiated mice and mice that have aged to 7 months, suggesting that neurogenesis rates are too low by early-middle age to have a behavioral impact [56]. Collectively, these data highlight the need to study older animals that

can better model adult humans, and they provide a fresh impetus for identifying strategies to enhance neurogenesis in older age.

While neurogenesis may decline early, this does not render irrelevant the large body of work that has identified important roles for new neurons in cognition and mental health. It is becoming increasingly clear that many mental health disorders, including those that involve the hippocampus, emerge prior to adulthood while the human brain continues to develop during childhood and adolescence [86–89]. Of all mental illnesses, DG neurogenesis has most consistently been linked to depression in animal models [90]. In humans, depression is often precipitated by early life adversity and can emerge in adolescence [89,91,92]. Similarly, DG neurogenesis is also implicated in anxiety, addiction, and schizophrenia [34,90,93], all of which are influenced by early life events and can arise prior to adulthood [94–96]. Thus, functions of neurogenesis, as identified in adult animals, remain relevant for understanding human disorders. However, given the timecourse of neurogenesis and the developmental trajectory of mental illness, greater emphasis on the relevance for younger humans is warranted.

Neuronal Development and Plasticity: Questioning the Critical Period

Immature DG neurons have distinct properties that could endow them with important behavioral functions. What happens as the cells mature? One possibility is that, upon reaching a certain age, DG neurons become comparable to the larger, older population. While mature adult-born neurons do share properties with mature developmentally-born neurons, there is emerging evidence that adult-born neurons have unique properties that extend beyond the traditional 4–6-week critical period.

The first line of evidence comes from studies of the maturation of neurons born at different stages of life in rodents. DG neurons born in adulthood mature slower than neurons born in early postnatal development [97], and this pattern continues throughout adult life: neurons born in middle-aged mice (8–12 months) extend dendrites, and gain spines and functional synaptic inputs at slower rates than neurons born in young adult mice [98]. Twelve-day-old neurons also have larger dendritic trees in young adult rats than in middle to old-aged rats, suggesting prolonged development with age [73]. Thus, while fewer neurons are added with age, they retain distinct properties and may provide significant plasticity for longer portions of the lifespan.

A second line of evidence comes from studies of experience-dependent modification of adult-born neurons. Initial studies reported that spatial water maze training increases the dendritic length and spine density of 1-week-old adult-born neurons in rats, but not putative older neurons [99]. Subsequent work revealed that enhanced structural plasticity is also observed in 2- and 4-month-old adult-born neurons, and that removal of these older cohorts of adult-born cells impaired learning [100]. Our own unpublished work also reveals that, while 4-week-old adult-born neurons in rats are structurally comparable to neurons born in infancy, growth of spines and presynaptic terminals surpasses infant-born neurons if examined at later intervals, when cells are 2–6 months old. Collectively, these data raise fundamental questions about exactly how long new neurons retain enhanced plasticity and they suggest that important functional roles of newborn neurons may persist much longer than is generally appreciated.

Recalibration Based on the Speed of Neuronal Maturation

While the full timeframe of new neuron development is unknown, some cellular features are clearly limited to defined windows of immaturity. Translating the developmental trajectory of

new neurons across species is therefore necessary to determine the timeframe of new neuron functions in humans (Figure 1). This is difficult because there are few precise non-rodent studies of DG neuron development. However, clues from longer-lived mammals suggest that neuronal maturation is likely to be longer in humans than mice and rats. Naked mole rats, which live up to 30 years, undergo extended development and retention of immature neural features compared with mice [101,102]. Red foxes also have disproportionately high numbers of doublecortin-positive cells given their low rates of proliferation, suggesting prolonged maturation and/or preservation of immature features as a compensatory source of plasticity [103]. In mice and rats, doublecortin is primarily expressed for the first 2–3 weeks of neuronal development [104] but in primates it is expressed for at least 6 months [62,91]. This is a ~10× difference in duration, which also approximates the difference in lifespan between primates and rodents. Applying this rule to the critical period for enhanced LTP (~6 weeks [40]), newborn DG neurons might be expected to have enhanced synaptic plasticity for over a year in primates and even longer in humans. Similarly, if the enhanced capacity for morphological plasticity, which lasts at least 4 months in rats [100], is scaled according to human lifespan (30×), DG neurons in humans would be expected to retain this heightened plasticity for at least a decade.

The data suggest that even DG neurons born in childhood in humans could retain unique functions in adolescence and adulthood. Indeed, other aspects of human neurodevelopment, such as the pruning of prefrontal neurons, extend well into adulthood [105]. A similarly long period of development may also apply to the human DG. Calbindin expression patterns, as a crude measure of neuronal maturity, indicate that human DG neurons develop over the first decade of life [106]. Neuroanatomical gradients of calbindin loss suggest that later-born neurons in the adult human DG are more vulnerable to epilepsy-related damage [107]. Finer aspects of maturation may occur over even longer intervals, as suggested by observations that DG neuron dendrites do not reliably reach the hippocampal fissure in primates as they do in rodents [108–110]. Quantitative support comes from reports that human DG neurons continue to extend dendrites through old age [111,112]. In this context it is notable that Alzheimer's pathology can begin in the upstream entorhinal cortex long before old age [113]. Thus, the prolonged 'development' of late-generated DG neurons could overlap with disorders that emerge many years after they were born.

DG Neurogenesis and Ontogenetic Diversity

Neurodevelopmental studies often characterize the spatiotemporal patterns by which different cell types are generated. For example, the excitatory neurons of the different layers of the neocortex are comprised of distinct populations that are generated sequentially and in a stereotyped fashion. Despite originating in the same germinal zone, neurons in the various layers are functionally distinct in their physiology and circuit connectivity [114]. This persistent form of cellular heterogeneity is distinct from the maturation-based heterogeneity described above because differences do not disappear as cells age, but depend on when in the lifespan the cell was born.

While appearing homogeneous upon superficial inspection, pyramidal neurons in the hippocampus also display a surprising degree of variation that depends on neurodevelopmental timing. In CA1, pyramidal neurons are arranged in layers that are generated at different stages of development and have distinct morphology, connectivity, and behavioral functions [115,116]. In CA3, a unique subset of highly-active pyramidal neurons are generated in a brief, early window of prenatal development [117]. Developmental timing also dictates intrahippocampal connectivity, where subcircuits of

preferentially-connected neurons are embedded in the trisynaptic pathway based on neuronal birthdate [118].

Despite its protracted development, the role that ontogenetic timing plays in DG cellular heterogeneity is surprisingly underexplored. In rodents and primates, DG neurons are added along ventral to dorsal, suprapyramidal to infrapyramidal, and superficial to deep gradients [119,120]. Patterns of activity-dependent gene expression [121], morphology [122], physiology [123], and behavioral functions [124] vary across the same gradients, broadly linking cellular properties to developmental birthdate.

More precise ontogenetic relationships are only beginning to be investigated. By tagging age-defined cohorts of DG neurons, it was recently revealed that physiologically-distinct semilunar granule cells [125] are born around embryonic day 14 in mice [126,127], and their dendritic patterning is substantially different from neurons born just a few days later, on the day of birth [127]. Early work demonstrated that superficially-located, presumably older, cells in rats have more primary dendrites, greater total dendritic length, and broader dendritic arborization [122]. The ontogenetic basis of many of these morphological differences was recently confirmed [127]. Given the important role of dendritic architecture in integrating/processing synaptic inputs [128], this suggests that DG neurons are likely to perform distinct computational functions based on their birthdate. Indeed, reconstruction of recorded DG neurons has revealed that neurons with higher-order dendritic branching patterns are preferentially active during spatial navigation [129].

The extent to which adult-born neurons are fundamentally different from other neurons, or simply in a protracted stage of development, is unclear. Some observations suggest that functional differences may extend into cellular maturity, arguing in favor of the former scenario. For instance, 4-month-old adult-born neurons in rats show unique patterns of experience-dependent zif268 expression relative to 4-month-old infant-born neurons [130]. Differences may also extend to cells born at different times in adult life, as old neurons born in young adult rats show greater zif268 expression than old neurons born in middle-aged rats [131]. Patterns of neuronal persistence also suggest fundamental differences: adult-born neurons in rodents survive indefinitely once they have reached 4 weeks of age [132,133] but some infant-born DG neurons die off between 2 and 6 months of cell age [133,134]. Finally, some superficially-located neurons, which are unlikely to substantially differ in age, are capable of synaptic LTP whereas others exhibit none [37,40].

In summary, cell age cannot fully explain differences in cellular properties between DG neurons. Instead, heterogeneous properties depend, at least in part, on when in the lifespan a neuron was born. Future work can examine if neurodevelopmental timing can explain other intriguing types of heterogeneity in the DG, such as neurons with twice the normal spine density [108,109,135] and neurons with unusually long and plastic mossy fiber extensions [136].

Recalibrating According to Ontogeny

How might the relative timing and order in which neurons are generated result in meaningful, persistent functional differences between cells? One possibility is that protracted DG neurogenesis is needed to produce a continuous gradient of cell types. For instance, a continuum of anatomical and physiological differences could facilitate the separation of cortical input patterns, one of the hypothesized core functions of the DG in memory [137]. A similar argument has been put forth based on patterns of gene expression across hippocampal neurons [138],

where graded differences in cell type may help tune neuronal receptive fields to the array of incoming sensory signals.

Another possibility is that there are more fundamental differences in DG cell types. For example, differences in immediate-early gene expression and morphological plasticity are likely to impact memory storage [92,122,123,131], and differential susceptibility to cell death might underlie distinct roles in memory turnover [133,134]. It is unknown whether differential connectivity with medial and lateral entorhinal cortex persists or disappears as new neurons mature [139,140]. This question is significant because these subregions provide the hippocampus with the contextual and content-related components of experience, respectively [141]. Unique connectivity will therefore dictate which aspects of sensory experience DG neurons are responsive to.

Finally, the vast majority of psychiatric and neurological disorders are associated with cell type-specific vulnerability. For example, aging and Alzheimer's disease are associated with specific loss of layer 2 entorhinal cortex neurons [142,143]. Nigral dopaminergic neurons, and other specific cell types, are highly vulnerable in Parkinson's disease [144]. Cellular heterogeneity in the DG may therefore result in some populations being more vulnerable than others to various pathologies. Furthermore, impaired neurogenesis may be involved in the reduced hippocampal volume that is observed in disorders such as depression [145], schizophrenia [146], mild cognitive impairment [147], and Alzheimer's disease [148]. However, given the unique pattern of delayed death of earlier-born DG neurons in rats [133,134], it is also possible that earlier-born cells are more vulnerable to pathology. Indeed, in a mouse model of Alzheimer's disease, superficially-located, presumably earlier-born, neurons undergo greater dendritic atrophy [149]. Finally, in the context of epilepsy, given the different electrophysiological profiles and activity patterns that have been observed in DG neurons, it is also plausible that subpopulations of neurons differentially contribute, or are vulnerable, to seizure-related hippocampal damage [150].

Concluding Remarks and Future Perspectives

Reports of limited neurogenesis in adult humans have been difficult to reconcile with animal work demonstrating persistent neurogenesis throughout life, and with human studies arguing for lifelong neurogenesis. Our review suggests that, once developmental timing is accounted for, the human and animal literatures are generally consistent with one another: the human hippocampus develops largely prenatally, leaving less opportunity for postnatal neurogenesis. In contrast, the rodent DG forms postnatally and is typically studied in adolescence and young adulthood, when neurogenesis rates remain high. Thus, some confusion has arisen as a result of modeling adult humans with juvenile rodents. While it remains unresolved whether neurogenesis drops to zero in adult humans, our comparative analysis suggests that it falls to low rates for much of adult life in all species.

What then is the relevance of adult neurogenesis for humans? Our review offers several perspectives for interpreting the literature and guiding future research questions. First, low rates of neurogenesis in adulthood, over years and decades, may have substantial additive effects that promote long-term health. Second, higher rates in early life may play a significant role in childhood and adolescent brain function, when many mental health disorders originate. Third, an ontogenetic perspective may help identify heterogeneous cell types in the DG, and how they differentially contribute to health and disease. Uncertainties about human–animal differences, and the extent to which cellular properties reflect maturational states versus persistent features, also highlight opportunities for future research (see Outstanding

Outstanding Questions

How many subpopulations of DG neurons exist, and how can one define them? In some instances, such as the semilunar granule neuron, the birthdate, morphology, and physiology are defined and distinct. In contrast, while old adult-born neurons differ from infant-born neurons in immediate-early gene expression and morphological plasticity, the corresponding physiological properties remain unknown. Given that neurogenesis may also interact with other lifespan processes (e.g., hormones and environment) a fuller understanding requires a detailed investigation of neurons born at different stages of life.

Which properties of newborn neurons are due to their immature state and which are permanent features? Properties related to cellular development can be expected to disappear with time and age, as neurogenesis declines. In contrast, permanent features would lead to functions that persist throughout the lifespan. With this knowledge, one could make better predictions about how neurogenesis could be harnessed to improve health throughout life.

How can we better model human DG neurogenesis? Transgenic mouse models are invaluable for studying age-defined cohorts of DG neurons and addressing mechanistic questions, but their translational relevance is limited, partly due to neurodevelopmental differences. Conversely, primates present a closer model for some aspects of human neurogenesis, but are often costly and time-consuming, and for certain applications can be ethically challenging. Shorter-lived animals that are born with a relatively mature brain, or primate models such as marmosets that are experimentally more practical, may provide new insights into the nature of human DG neurogenesis.

Can the age-related decline in neurogenesis be reversed or offset? This is an ongoing pursuit, and the low neurogenesis observed in aged rodents makes them a suitable model for this problem.

Cell types are often defined by differences in gene expression. Do DG

Questions). In summary, consideration of the broader neurodevelopmental context will help us take advantage of the benefits that neurogenesis may offer for human mental health.

neurons of different ages, and ones born at different stages of the lifespan, have unique genetic signatures? If so, this could lend support to the ontogenetic diversity model, and facilitate strategies for targeting neuronal populations in animal models and possibly for treatment of human disorders.

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