OPINION

New neurons for 'survival of the fittest'

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Abstract | Adult neurogenesis is often considered an archaic trait that has undergone a 'phylogenetic reduction' from amphibian ancestors to humans. However, adult neurogenesis in the hippocampal dentate gyrus might actually be a late-evolved trait. In non-mammals, adult hippocampal neurogenesis is not restricted to the equivalents of the dentate gyrus, which also show different connectivity and functionality compared to their mammalian counterpart. Moving actively in a changing world and dealing with novelty and complexity regulate adult neurogenesis. New neurons might thus provide the cognitive adaptability to conquer ecological niches rich with challenging stimuli.

Adult neurogenesis is widespread in the animal kingdom, and it is often stated that it was gradually lost during the course of evolution[1,2]. With increasing sophistication of the brain during the course of evolution, so the reasoning goes, natural selection favoured neuronal networks with fixed numbers of neurons over networks with a sustained resupply and thus eliminated adult neurogenesis. The assumption is that complex brains require stable conditions and would not be able to cope with the degree of plasticity introduced by new neurons. Indeed, most mammals possess only two 'canonical' neurogenic regions (whereas adult zebrafish have 16 (REF. 3)): the subventricular zone (SVZ), which provides new interneurons to the olfactory bulb, and the subgranular zone (SGZ) in the hippocampal dentate gyrus (for a detailed review, see REF. 4). A review from 2006 (REF. 2) presents an extensive overview of the available literature on adult neurogenesis across numerous species, identifying the need for a framework for the evolution of adult neurogenesis, and several articles have discussed the evolution of adult neurogenesis[5–10]. More recent reviews have also taken up the issue[11,12], and the idea of a decline in neurogenesis through evolution can be found in all of these considerations. In this Opinion article, I argue that although adult neurogenesis in general might be an ancient trait, adult neurogenesis in the hippocampus gained a novel, specific relevance with the evolution of the dentate gyrus in mammals. I argue that adult hippocampal neurogenesis is a late-evolving trait and that it lies at the heart of the functionality of the dentate gyrus. This does not imply that the dentate gyrus works only through new neurons; rather, I propose that possessing a dentate gyrus with the particular type of plasticity provided by adult neurogenesis might have given a particular advantage in the ability of mammalian species to adapt to their environment. Adult hippocampal neurogenesis might be advantageous because it allows activity-dependent network optimizations that increase cognitive flexibility and hence, presumably, adaptability (that is, the "capability of an individual to meet a new challenge set by the environment" (REF. 13)). My argument arises from a neuroscience perspective on adult neurogenesis and aims to present a first attempt at an ecological perspective, which is currently not present in the neurogenesis field. This hypothesis does not constitute a comprehensive 'evolutionary theory of adult neurogenesis'. For such a broader ecological perspective, we lack data and, at the moment, the inclination of evolutionary biologists to choose 'adult neurogenesis' as a topic of interest. My hope is that this article will help to motivate such research.

Pressure against adult neurogenesis?

The presumed evolutionary loss of widespread adult neurogenesis has been termed a 'phylogenetic reduction'. Although the idea has merit, two issues complicate the matter. First, only species living today have been studied and, as there is no fossil record of new neurons, we do not know whether adult neurogenesis existed in common ancestors. Second, even of the currently living species, few have been examined (FIG. 1). Our knowledge comes mainly from studies on inbred or domesticated species, as these outnumber studies on wild species by far.

Comparing levels of adult neurogenesis between species is a major challenge. Numbers of proliferating precursor cells, for example, are poor predictors of neurogenesis, even within one species[14]. The commonly used measure of doublecortin (DCX)-expressing cells as a proxy for adult neurogenesis captures both advanced precursor cell stages and early postmitotic stages of development but does not extend to the fully mature, integrated new neurons or the radial glia-like stem cells. This measure is strongly affected by the duration of the period during which DCX is expressed during the course of development[15]. Another issue is the question as to what any number indicative of new neurons should be compared. The number of granule cells has been proposed as a denominator, but whether a ratio of 'new neurons' over granule cells is functionally relevant and stable across species is not known. Age is a factor that influences the rate of adult neurogenesis in most species that have been studied, but the question as to what age could serve as a standard age for comparison is not trivial, as age-related differences in levels of adult neurogenesis could mask or exaggerate species differences. Last, the relationship between the quantity of adult neurogenesis and its functional relevance might not be linear, neither cross-sectionally between species (and possibly even individuals) nor longitudinally over the lifespan of one species. If adult hippocampal neurogenesis indeed serves to cumulatively optimize the neuronal network to cope with changing functional needs, experienced old individuals should have an optimized dentate gyrus

with little ongoing adult neurogenesis but with a preserved potential for further optimization in (the increasingly fewer) situations that are novel[16].

Even if, for the sake of argument, these issues are put aside, the apparently simple idea of phylogenetic reduction is full of holes. *Drosophila melanogaster* for example, does not have any adult neurogenesis under normal conditions[17]. Neurogenesis in the mushroom body is found in some insect classes but not in others[5]. Crustaceans do

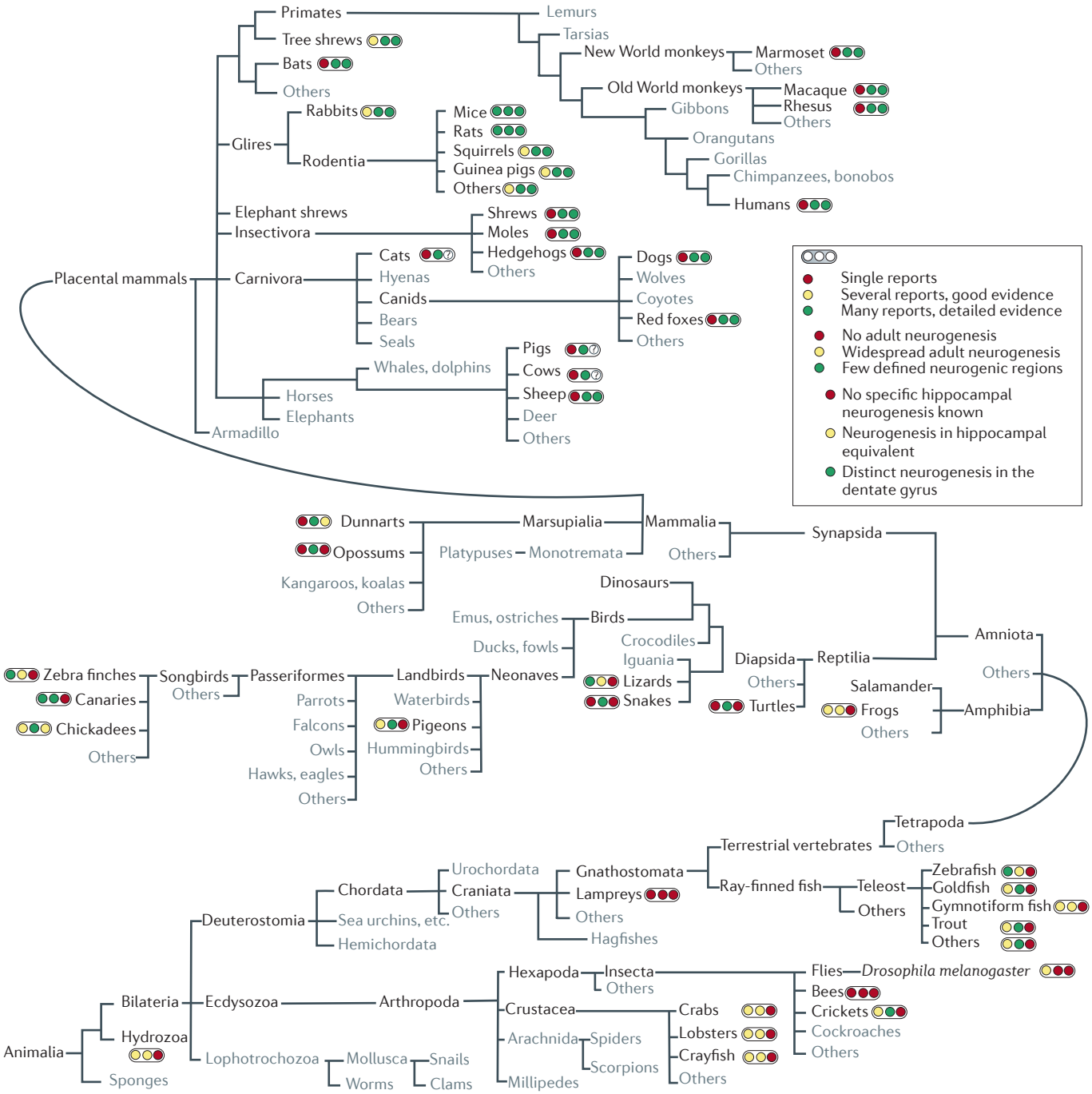

Figure 1 | **Phylogenetic map of adult neurogenesis.** Adult neurogenesis can be found throughout the animal kingdom, but many branches of the phylogenetic tree and a very large number of species have not yet been studied. In non-vertebrates and lower vertebrates (lower third of the figure), the level of adult neurogenesis, as far as it is known, varies greatly between species (and it is often difficult to define 'adulthood' in these species anyway). It is best studied in fish, in which numerous neurogenic regions are found. In reptiles and birds (middle third), adult neurogenesis is spatially more confined than in lower vertebrates but still highly variable. Like fish, birds have a cortical structure that corresponds to the hippocampus of mammals, but they do not have a dentate gyrus (DG) proper and there is no concentration of neurogenesis in the equivalent area. In marsupials, interestingly, the pattern seems to be identical to that in placental mammals (upper third). In placental mammals, adult neurogenesis is essentially confined to the two 'canonical' neurogenic regions in the olfactory system and the hippocampus. Mammals all seem to have a hippocampus with a dentate gyrus of particular form, connectivity and function (FIG. 2). The phylogenetic information has been taken from The Tree of Life Web Project[87].

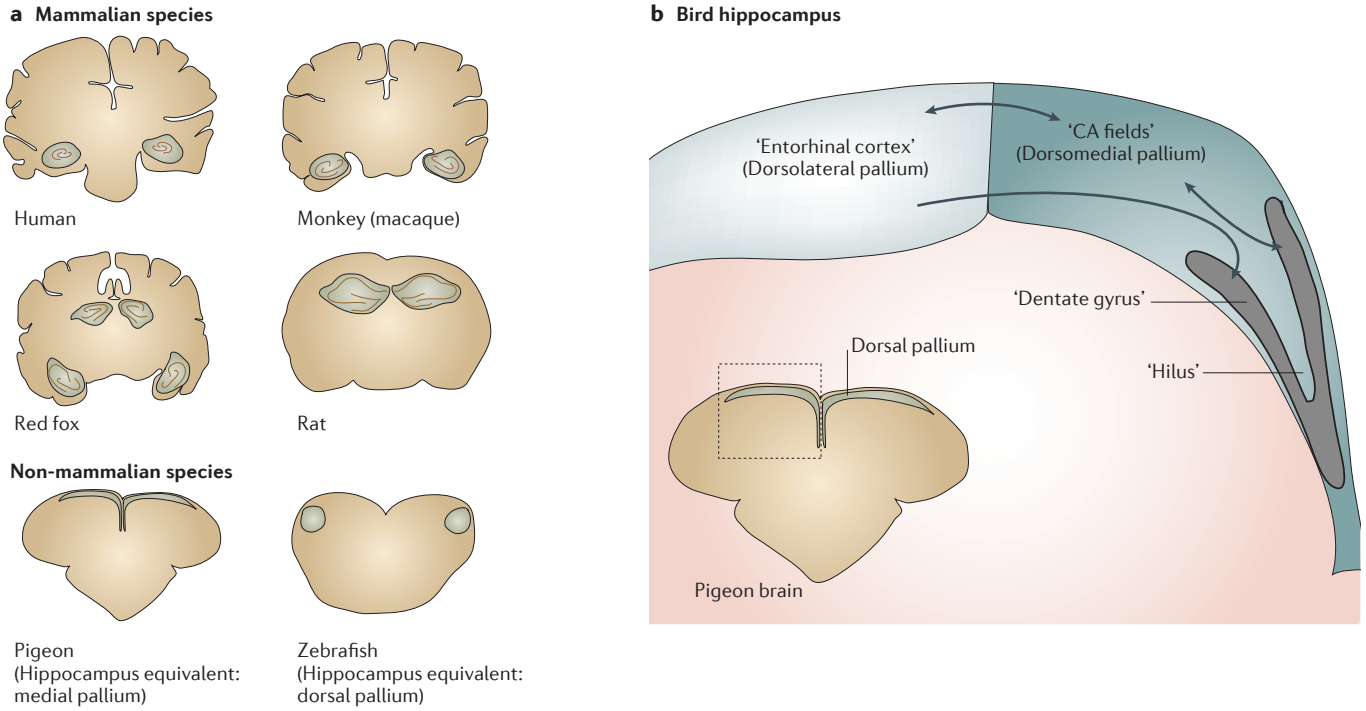

Figure 2 | **Phylogenetic comparison of the hippocampus. a** | In all studied mammals, the hippocampus has an essentially identical structure and contains a dentate gyrus of similar appearance. Hippocampal neurogenesis in all mammals appears to be restricted to the dentate gyrus. During mammalian evolution, the hippocampus underwent a complex 'displacement' and rotation as a consequence of the increase in the size of neocortical regions. Thus, in humans and macaque monkeys, the hippocampus is located near the base of the brain, whereas in rodents it is still located much more dorsally. The fine anatomy, however, is strikingly similar in primates and rodents. In foxes, the hippocampus is stretched between the dorsal and ventral parts of the brain. In non-mammalian species, the hippocampus equivalent is found below the dorsal surface of the brain. In lizards, for example, the medial cortex represents the analogue to the dentate gyrus and also shows adult neurogenesis, which, unlike in mammals, is not restricted to that hippocampal subregion[88,89] (not shown). In zebrafish, the most lateral portion of the dorsal pallium is considered to be the 'predecessor' of the dentate gyrus[90]. **b** | In birds, the medial pallium provides functionality that in mammals is provided by the hippocampus; for example, it has a role in spatial navigation. At the fine-structural level, a V-shaped cell band towards the midline (dark grey) might represent the bird 'predecessor' of the dentate gyrus, although there is some disagreement about the interpretation of this band of cells. The connectivity of these cells (indicated by the arrows) is different from that of the dentate gyrus in mammals, in the sense that there is no mossy fibre tract and the link between the dentate gyrus and the CA homologues is bidirectional in birds (indicated by the arrow) but not in mammals[70].

not seem to have more than two neurogenic zones; they show robust adult neurogenesis in the olfactory system (but only in two studied species) and in the optic stalk[18]. Results from fish species are highly variable as well[1]. Frogs and other amphibians have little adult neurogenesis[11], but most bird species have rather a lot [12].

Rodents and primates might show a sizable level of adult neurogenesis in only two regions, but thorough studies indicate that rabbits have more neurogenic zones[19] and most (but not all) bat species have only one (the SVZ but not the SGZ)[20]. The very limited data from hamsters[21], guinea pigs[22], cows[23] and marsupial species[24] do not yet allow a conclusive picture but also do not suggest that there is a correlation between brain complexity and adult neurogenesis. Thus, although regenerative capacities and adult neurogenesis do differ across the animal kingdom, only a handful of species have been thoroughly studied, and it therefore seems premature to conclude that there is an evolutionarily determined, relative general loss of adult neurogenesis in primates and humans.

For humans, strong direct and indirect data support the existence of lifelong adult neurogenesis in the hippocampus[25,26] but suggest its almost complete absence in the olfactory bulb after childhood[27–29]. The available information, however, does not indicate that adult neurogenesis in humans is fundamentally different from that in mice and rats, by far the best-studied mammalian species. Nonetheless, there are some important differences; for example, humans have a conspicuous hypocellular 'gap' in the SVZ that they share with rabbits and cows but not with rodents[30], the human SGZ is less sharply delineated than the rodent SGZ and neurogenic precursor cells in the human SGZ appear to be found in a wider zone than in the rodent SGZ. But differences in detail alone do not make a strong case against the phenomenon of lifelong adult neurogenesis in humans.

Are new neurons advantageous?

What distinguishes an 'advanced' brain from a simpler one? In 1985, Pasko Rakic published an important and influential article[31] in which he argued why there must be limits to adult neurogenesis in primates. At the heart of this argument is the 'stability–plasticity dilemma', for which every learning network must find a solution. Networks that are too stable cannot acquire anything new, whereas networks that are too flexible cannot remember because they cannot lastingly store information. According to this concept, the addition of new neurons would disrupt complex neuronal networks, such as the primate and human neocortex. However, computational modelling studies have demonstrated that certain networks not only can cope with but even require new neurons. It has been argued that adult neurogenesis allows a particular solution to the stability–plasticity dilemma that is tailored to the dentate gyrus[32], and that the neocortex and

other non-neurogenic regions seem to have realized different solutions by relying on other types of plasticity. It might well be the case that new neurons would be disruptive in these regions; as the exact computational problems differ between brain regions, different solutions to the stability–plasticity problem may have co-evolved.

In terms of computational power per neuron, simple brains can perform very complex tasks. For example, the ant brain can solve the amazingly difficult problem of spatial navigation in the desert[33]. Importantly, however, it does not have the flexibility to do so when an ant is exposed to a different environment. Thus, it seems that the simple brain is hardwired for its task, whereas the complex brain is flexible and plastic. The conquest of dry land by our reptilian ancestors was associated with a massive growth in brain size, computational power and plasticity. Mammals can learn more than any fish, even though the general Hebbian principle that underlies learning is the same.

Why, then, should phylogenetically 'old' and hardwired brains, as a rule, have more adult neurogenesis than 'newer' brains, the primary principle of which appears to be plasticity and adaptability? It seems that the reverse of the phylogenetic reduction argument actually makes a stronger hypothesis: it is the high degree of plasticity in the mammalian brain that has allowed unsurpassed environmental adaptation for most of its species, and this plasticity includes adult neurogenesis.

The dentate gyrus evolved late

The idea that neurogenic zones 'dried up' during evolution is contradicted by the fact that one of the two brain structures that show adult neurogenesis in rodents and primates does not exist in this form in lower vertebrates[34]. The hippocampus is an ancient part of the brain but the dentate gyrus is a more recent addition. Although fish, amphibians, reptiles and birds possess an equivalent to the hippocampus, the existence of a structure of comparable functionality to the dentate gyrus of mammals is more questionable (FIG. 2; BOX 1).

The classical nomenclature reserved the term 'hippocampus' (proper) for the CA fields and the subiculum. Development of the dentate gyrus is complicated, occurs largely separately from the rest of the hippocampus and involves an ectopic precursor cell population that becomes displaced from the ventricular wall[35]. That the dentate gyrus is an 'add-on' is also visible in the fact that, to a certain degree, input from the entorhinal cortex to CA3 bypasses it (FIG. 3). The dentate gyrus consists of principal neurons that project to only one target: CA3. However, the medial perforant path from the entorhinal cortex also directly connects to CA3 (REF. 36), so that the classical trisynaptic circuit in fact has a bisynaptic backbone. Activity within this connection even precedes activation in the connection via the dentate gyrus[37,38], so that CA3 first learns about novel input through the direct connection rather than from the dentate gyrus[39]. Thus, the synapse in the dentate gyrus lies within a collateral structure and is both a phylogenetically and ontogenetically (as it is partly produced by adult neurogenesis) more recent addition to the circuit.

This connectivity and the widespread modulatory input that it receives make the dentate gyrus perfectly suited as a supervising and regulatory structure, and the new neurons might be the "new gatekeepers at the gateway to memory" (REF. 40).

The key to understanding adult hippocampal neurogenesis thus lies in understanding the evolutionary advantage associated with having a dentate gyrus of the kind mammals have. Could neurogenesis in the adult hippocampus not be a newly evolved form of plasticity that builds on ancient mechanisms? It is possible that it was the novel form of plasticity realized through adult hippocampal neurogenesis that helped to make the mammalian hippocampus so uniquely powerful and that provided one important advantage in evolutionary adaptability. This is not to say that mammals evolved to what they are today only because of their dentate gyrus or only because of adult neurogenesis. Instead, the idea I propose is that a hippocampus that includes a dentate gyrus of mammalian structure and function, which provides neurogenesis-related plasticity, might enable a greater potential for flexible adaptation than one without.

The function of the dentate gyrus

With regard to the functional relevance of the hippocampus, we might often be misled

Box 1 | Evolution of the hippocampus and the dentate gyrus

An important argument in the idea that adult hippocampal neurogenesis evolved late is that non-mammals do not have a dentate gyrus with the same specific characteristics and consequently lack the structure and exact functionality to which the adult-born neurons would add[34]. The mammalian dentate gyrus had its predecessors, and there are equivalent structures in birds, fish and lizards, but there is no dentate gyrus of the mammalian form, structure and — as far as this has been studied — connectivity 'below' monotremes[67]. Hippocampal growth increased with the evolution of the corpus callosum[68].

Unfortunately, there is little literature on the detailed comparative anatomy of the hippocampus, and most available information stems from before the days of immunohistochemistry, fibre tracing, electrophysiology and genetic reporter constructs. More details are clearly needed. In mammals, the distinctive gross structure of the hippocampus is similar between species, but there is a wide range of detailed species-specific morphologies[69]. After mammals, most information comes from birds, for which the picture is even less homogeneous and no agreement about the homology of substructures has as yet been found[70].

In non-mammals, the primordial hippocampus is a single band of neurons in the lateral pallium in fish, amphibians and reptiles and the medial pallium (below the dorsomedial cortical surface) in birds. With the development of the neocortex and the large commissural connection between the two hemispheres in mammals, the primordial hippocampus was rotated and pushed deep into the temporal lobe[69].

A deceivingly obvious candidate analogue for the dentate gyrus in birds is a V-shaped structure in the medial cortex (FIG. 2), but the connectivity of this structure is different from the connectivity of mammalian dentate gyrus, and there is no bundled mossy fibre projection[70]. Others have considered this V-shaped structure as corresponding to the CA fields and the dorsomedial parts as corresponding to the dentate gyrus[71]. At the cellular level, no obvious distinction between granule cells (of the dentate gyrus) and pyramidal neurons (of the CA fields) is possible in birds, so that no clear boundary can be set. Adult neurogenesis has been described in the 'hippocampus' of birds, but the new cells were found throughout the structure rather than refined to a substructure that could be analogous to the dentate gyrus; in addition, newborn neurons were found alongside the lateral ventricle[72].

A growing rather than shrinking functional relevance of the hippocampus is also supported by the fact that within primate species, the dentate gyrus continues to increase in size from insectivores to humans. It has been estimated that humans have a hippocampus that is approximately 4.2 times as large as that of primitive insectivores of (theoretical) equal body weight[73]. The dentate gyrus shows an enlargement by a factor of 2.6, and the greatest change is seen in CA1, with an enlargement by a factor of 6.6.

by the fact that much of our knowledge stems from studies that assessed hippocampal function as underlying spatial memory in rodents. But the hippocampus is not just for space[41] or spatial learning per se (for which adult neurogenesis is not needed)[42]. Laboratory rodents might not be the best species to further elucidate the ethologically relevant aspects of this function. Few studies have addressed adult neurogenesis in wild-living rodents (and these have shown considerable variation in the level of adult neurogenesis)[7,9], but functional aspects are challenging to approach in the wild. Nevertheless, a study in food-storing red squirrels indicated, for example, that different demands on spatial memory alone are not associated with different levels of adult hippocampal neurogenesis[43].

For rodents in captivity, a wealth of studies have clearly shown that the new neurons indeed serve specific functions. The diversity of approaches to manipulate adult neurogenesis and to measure behavioural outcomes increasingly precludes the possibility that all of these studies got it wrong. Although the emerging picture is still far from providing a unifying theory and many questions remain open, the idea that new neurons in the adult dentate gyrus are cognitively irrelevant can no longer be sustained. In fact, few phenomena in cognitive neurobiology have spurred a race that is comparable to the quest to identify the function of new neurons in the adult hippocampus.

One function of the dentate gyrus that could be linked to adult neurogenesis is 'pattern separation' — the ability to distinguish two pieces of information in time[44]. The key idea is that new neurons would be involved in 'time-stamping' new information. A related function is the association of information to contexts (which has mostly been studied with the paradigm of contextual fear conditioning)[45]. Garthe and I have proposed that adult neurogenesis is required to allow the flexible integration of important pieces of information into a previously learned representation[42]. This hypothesis makes reference to both pattern separation and contextualization of information. We speculated that such functionality would be particularly beneficial for those species (and individuals) that show the greatest adaptability to changing environments.

I propose that adult neurogenesis might be a phylogenetically old mechanism, but in the adult mammalian hippocampus, this primordial, stem cell-based mechanism was put to new use and was refined in a way that added an entirely new functionality to the

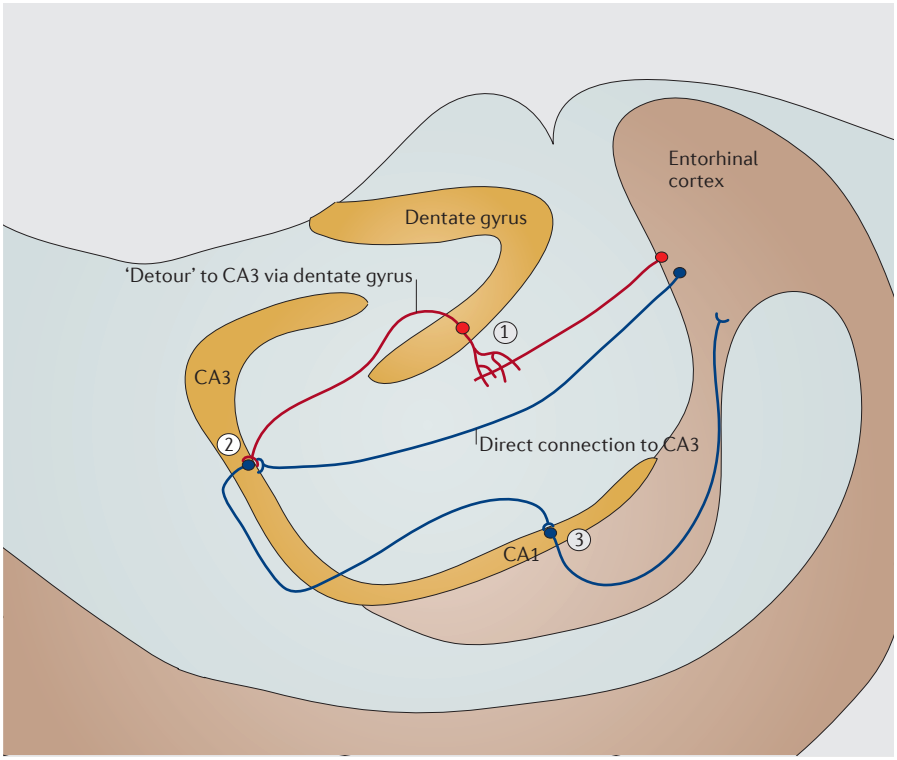

Figure 3 | **Simplified scheme of the basic circuitry of the hippocampus.** The backbone circuit of the mammalian hippocampus is usually described as trisynaptic, with the first synapse between the input from the entorhinal cortex and the dendrites of the granule cells of the dentate gyrus (1), the second synapse between the mossy fibres (the axons of the granule cells) and the pyramidal neurons of CA3 (2), and the third synapse between the axons of the CA3 pyramidal neurons and the pyramidal neurons of CA1 (3), which then again project out to the subiculum and the entorhinal cortex. However, a direct connection exists between the entorhinal cortex and CA3, and input through this connection reaches CA3 faster than input via the dentate gyrus. The link via perforant path, dentate gyrus and mossy fibre tract (shown in red) is thus a 'detour', and adult hippocampal neurogenesis may fine-tune this additional circuit.

structure — a functionality that would not have been achievable with the other available means of brain plasticity at the level of neurites and synapses alone (cellular structures that provide plasticity ubiquitously, from *Aplysia californica* to humans).

This new use of adult-born hippocampal neurons is fundamentally different from the function of new neurons in 'lower' animals and new neurons originating in the second neurogenic region of the adult mammalian brain — the olfactory system, a site in which neurogenesis is encountered in essentially all species that have been studied so far. Indeed, it might be counterproductive to consider adult neurogenesis in the hippocampus and the olfactory bulb together just because both regions generate new neurons. There are numerous differences[46]. For example, adult olfactory bulb neurogenesis generates several types of interneuron, whereas adult neurogenesis in the hippocampus produces only one type of excitatory principal neuron, which adds to the central mossy fibre connection between the dentate gyrus and CA3. New neurons in the olfactory bulb modify output, whereas new neurons in the hippocampus provide input connections. Neurogenesis in the olfactory bulb is dependent on the turnover of sensory receptor neurons in the olfactory epithelium and might be a way of stabilizing the network in the first sensory relay station in the face of this constantly varying input, whereas in the dentate gyrus there is only some turnover of immature neurons — this turnover appears to provide a functional benefit of its own, but generally the survival of newborn neurons is lasting and adult-generated hippocampal neurons contribute to a large proportion of the total granule cell number[47].

As adult hippocampal neurogenesis is regulated by behaviour and activity, most notably learning itself, I have proposed that adult hippocampal neurogenesis provides a means of optimizing the strength of the mossy fibre connection to the level of challenges encountered by the individual[40]. For

some as yet unknown reason, this connection needs to be as lean or sparse as possible but at the same time has to be as strong as is needed to perform the task. Neurogenesis might be centrally involved in such network optimization by titrating connectivity to meet specific computational demands. If this assertion is correct, the qualitative impact of adult neurogenesis would depend not only on quantitative measures of neurogenesis but also on the connectivity and contribution of the new neurons to an altered, presumably improved, network architecture. The relationship would therefore not be linear.

Adult neurogenesis means that the development of the dentate gyrus never ends. This brings to mind Flechsig's rule from 1901, which, in the paraphrasing words of Lipp, states that "the hierarchical status of brain systems is reflected by their maturational sequence during ontogeny (for example, Flechsig defined the association cortices as the cortex regions with the most delayed onset of myelination), and corresponds to the familiar phenomenon that 'simple' behavioural patterns and capacities appear earlier in ontogeny than the more 'complex' ones" (REF. 48). All the available evidence indicates that new neurons make such highly specific and advanced contributions to the functionality of the dentate gyrus. The dentate gyrus adds complex functionality to the hippocampus and thereby sets mammals apart from other animals. According to this interpretation, adult hippocampal neurogenesis takes place in a brain region that ranks highly in the functional hierarchy of the brain. Persisting neurogenesis in a structure that evolved late and develops late might imply that, here, the existing tool of adult neurogenesis was adopted to solve a new problem that is relevant for the high position of the dentate gyrus in the functional hierarchy of brain regions.

Adult neurogenesis and physical activity

Brains evolved with motility. Plants, corals and fungi do not need brains. Parasite species that are passively transmitted and become stably associated with their host lost the brain that their ancestors already possessed and that their moving relatives still have. Accordingly, the only kind of output that all brains are able to achieve is motoric, including human communication, speech and writing. Consequently, the idea that motoric output should strongly feed back upon the brain seems plausible.

When comparing motility between species, at the upper end of the evolutionary spectrum we find humans, with their extreme range of motility and their large brain. The ability to move almost everywhere (even reaching the moon) represents the most extreme expansion of the habitat. Notably, a large and highly variable habitat is not identical to the size of the home range of individuals of a given species. Lipp's initial hypothesis that (rodent) species with larger home territories, which require more locomotion to be covered, would have more adult neurogenesis turned out to be incorrect[8,9,49]. Many migratory animal species cover huge distances and show remarkable navigational skills, but this does not necessarily imply that they can flexibly change routes, times and destinations as new challenges arise on their way. I propose that the evolution of adult hippocampal neurogenesis has facilitated the response to the variability of the habitat (and hence the activity required to master it) and to the exposure to unpredictable change.

Highly developed brains allow the use of past experiences to make predictions: the greater and more versatile the range of experiences, the better the prediction and the greater the survival advantage for that species. A common perception is that the massive expansion of our brains was also a consequence of the evolution of upright gait. There is no explicit theory along these lines attributable to particular authors, but if one still follows this reasoning, leaving the trees and the conquering of the wide plains of the savannas promoted encephalization, partly because the extended motility provided an increased number of challenging and unstable sensory inputs. Many studies on the effects of physical activity on human cognition revealed effects of cardiovascular activity but not, for example, of stretching exercises[50]. This could reflect a feedback mechanism by which the activated cardiovascular system, together with the increased proprioceptive and other sensory input that is associated with locomotion at higher speed, signals to the brain. The brain, in turn, interprets the strength of this stream of signals as an indication of the chance of encountering complexity in space and time. Changing places requires flexibility, and doing so at increased speed over prolonged periods of time (as found in tribal and modern endurance runners, or wheel-running or freely roaming rodents, if one wants to follow this argument) requires optimized pattern separation. The observation that a generic stimulus such as physical activity should stimulate a type of brain plasticity that is relevant for complex cognition — an observation that is perhaps counterintuitive at first glance — might thus ne explained by this testable theory.

Adult neurogenesis for adaptability

A phylogenetic reduction of neurogenesis as a law of nature would imply that adult neurogenesis must be low or even absent in primates and humans, and studies that suggest it is not are easy targets of (admittedly often valid) methodological concerns. This implication might hold for the olfactory bulb: several studies indicate that adult olfactory neurogenesis occurs at extremely low levels or might not exist at all in humans[28,29]. The body of data on adult hippocampal neurogenesis in humans is limited, but there is no reason to assume that improved methodology would only reduce false-positive results rather than decrease false-negative findings (BOX 2). The available data that withstand methodological critique actually do not draw a picture of very low adult hippocampal neurogenesis in humans. Ericksson's 1998 landmark study[25] found a substantial number of new neurons in humans up to 72 years of age, the oldest subjects investigated, using the benchmark methodology from rodent studies (that is, the birthdating of proliferating precursor cells with bromodeoxyuridine (BrdU) and immunohistochemical identification of their progeny as neurons). Many markers that are associated with adult neurogenesis in rodents, including proliferation markers, are expressed in the adult and old human dentate gyrus without being ubiquitously found elsewhere in the brain and without being aberrantly upregulated by pathology[26]. Neural precursor cells have also been isolated from the human hippocampus[51]. Methodological caveats must not be taken lightly, and some claims might not hold. However, focusing only on the imperfections of the methodology might cause one to miss the bigger picture.

As new opportunities to investigate BrdU-labelled human brain samples are unlikely to arise, further research on new neurons in humans must resemble the search for elementary particles, which are predicted and measured only from their consequences, not directly (BOX 2). But a theory of hippocampal function that includes adult neurogenesis should have more explanatory power than one without it, and such a theory can be put to the test.

If adult neurogenesis is indeed, as the rodent data suggest, linked to the efficiency of information processing and the flexibility to adapt to changing complex environments, adult neurogenesis in the dentate gyrus might have evolved with mammalian species

Box 2 | **How to assess adult hippocampal neurogenesis in humans**

There are few available studies that directly and indirectly support adult hippocampal neurogenesis in humans, and they give no indication of a fundamental qualitative difference to the situation in mice and rats. This is in some contrast to the situation in the olfactory bulb.

In a landmark study from 1998, Eriksson proved the existence of adult neurogenesis in the human hippocampus on the basis of the standards set by research in rodents[25]. A group of five patients with cancer had received a single bromodeoxyuridine (BrdU) infusion for tumour staging purposes, and the method that had been established for the analysis of adult hippocampal neurogenesis in rodents was applied to the post-mortem examination of these patients' brains. As BrdU is no longer used for tumour staging and its carcinogenic properties prevent its application solely for research, no other study will be able confirm or extend these findings with the same methodology. A large survey used markers that, in rodents, are associated with the intermediate stages of adult neurogenesis, and assessed their expression in the human brain across the lifespan between 0 and 100 years[26]. Doublecortin (DCX), which is used as marker for these stages, was used as lead antigen, and its colocalization with a total of 21 other markers was investigated. Essentially all marker combinations known from rodent data were also found in the human brain. As in rodents, there was a decrease in the number of both dividing cells and DCX-expressing cells. In addition, DCX colocalized with other markers: until around 45 years of age (that is, until the end of the reproductive period), DCX overlapped with all key markers of adult neurogenesis known from rodents.

Birthdating cells based on ^{14}C is possible owing to the peak of ^{14}C levels in the atmosphere (and hence in living cells) that occurred during the time of above-surface atomic bomb testing between 1946 and 1963 (REFS 74–77). A study using mass spectrometry to measure ^{14}C content in the DNA of neurons and compare it to other cell types first showed that although cortical neurons are generally as old as the individual, glial cells are not[78]. The existence of adult hippocampal neurogenesis has not yet been confirmed with this method, but the challenges associated with the sensitivity of mass spectrometry are extraordinary. In addition, the method cannot be combined with other markers and can only be applied post-mortem. An approach based on heavy water (deuterium ions), which could potentially be injected into humans and analysed in a similar manner, has been proposed, but the method has not yet been confirmed[79]. This method, too, would not allow combination with other strategies to gain more information about any newly generated cells.

The use of MRI blood flow measurements in the hippocampus has been proposed as a proxy for adult neurogenesis[80]. This study was given much attention, but the approach is problematic as a prospective tool because the supposed relationship (extrapolated from animal data) between neurogenesis and blood-oxygen-level-dependent measures follows a U-shape. To become useful, any MRI-based method would require validation studies that include an independent method of demonstrating adult neurogenesis. The same applies to magnetic resonance spectroscopy. One study described a presumably neurogenesis-specific peak at 1.28 ppm[81]. Although the peak itself has been replicated by others, it is now mostly thought to reflect apoptosis rather than neurogenesis[82]. The method has also been criticized because of the mathematical transformations necessary to see the signal.

that are generalists in terms of the niches they can occupy. There are indications of such a link in insects as well. Cockroaches, which have generalist feeding behaviour and are ubiquitous worldwide, show adult neurogenesis in their mushroom body[52]. Gyrification of the mushroom body in turn is linked to generalist feeding behaviour[53]. Although a causal link remains to be proved, this co-occurrence is suggestive of a link. Mammals covering narrow and stable niches might thus need less or no adult neurogenesis, whereas species such as rodents and, presumably, humans might rely on it. In many systems, plasticity decreases when environments become stable[54]. I suggest that whether mammalian species have high or low levels of adult hippocampal neurogenesis might not depend so much on their position on the evolutionary ladder but relates to their flexibility to adapt to new or changing habitats. However, taking the quantity of new neurons or dividing precursor cells as the only measures of adult neurogenesis ignores the quality of the newly established connectivity. The relationship between the number of new neurons and their functional benefit will be neither linear nor identical between species. Nevertheless, adult neurogenesis is variable in quantity between species, individuals and in time, and it is regulated by activity and learning in terms of the numbers of cells, not just their connectivity. The very essence of adult neurogenesis is that it leads to changes in neuronal numbers (that is, the nodes of the network), and it is exactly this fact that sets it apart from neuritic and synaptic plasticity (which represent the edges in the network). So, numbers are not meaningless but require careful interpretation. We have tried to model such interactions between numbers and function in order to see how, for example, turnover and addition of neurons might work together[47], but more theoretical and empirical work is needed to pindown this relationship.

With that caveat in mind, detailed studies indicate that adult neurogenesis in monkeys occurs only at a low level, although these studies were all performed in animals born and raised in captivity. Whether such monkeys might still make better use of their fewer new cells in the wild, we cannot say. For our closest relatives, chimpanzees and other apes, we do not have any information about adult neurogenesis. In any case, no matter how complex the habitats of these primate species, these animals are found only in a limited number of environments and seem less flexible in their adaptability to new ones. So, presumably, are bats, which, although they are found throughout the world, are extremely sensitive to changes in their environment. Despite being excellent navigators with large territories, they are, for example, endangered by modern windmills and roads that cut across their territories. As almost blind, flying nocturnals, they are badly adapted to the rate of change in the well-lit world of today. In terms of adaptability, they are more distant from us than rats and mice, with which we can share all habitats (including artificial habitats such as ships) and which have considerable amounts of adult neurogenesis. Rats do even better than mice in terms of adaptability and (at least in the strains that have been studied) have more adult neurogenesis[55]. Dolphins — certainly cognitively 'advanced' animals but with a more homogenous habitat than rodents — have a relatively tiny hippocampus and a very small dentate gyrus, given the size of their brain[56]. Rodents might provide better models of the human dentate gyrus, at least with respect to adult neurogenesis. This does not mean that rodents and humans are what they are only because they have adult neurogenesis; rather, it suggests that among the factors that made them highly adaptable species, adult-generated neurons in the hippocampus have a greater role than was previously assumed. The few species mentioned here do not yet make a complete case, and the correlation between adult hippocampal neurogenesis and adaptability rests on too few data points. But the concept can be used as a basis to generate predictions and obtain a fuller set of data from more species and in conjunction with relevant ethological and behavioural details.

A sensitive window for plasticity

Adult neurogenesis seems to influence hippocampal functioning through two distinct

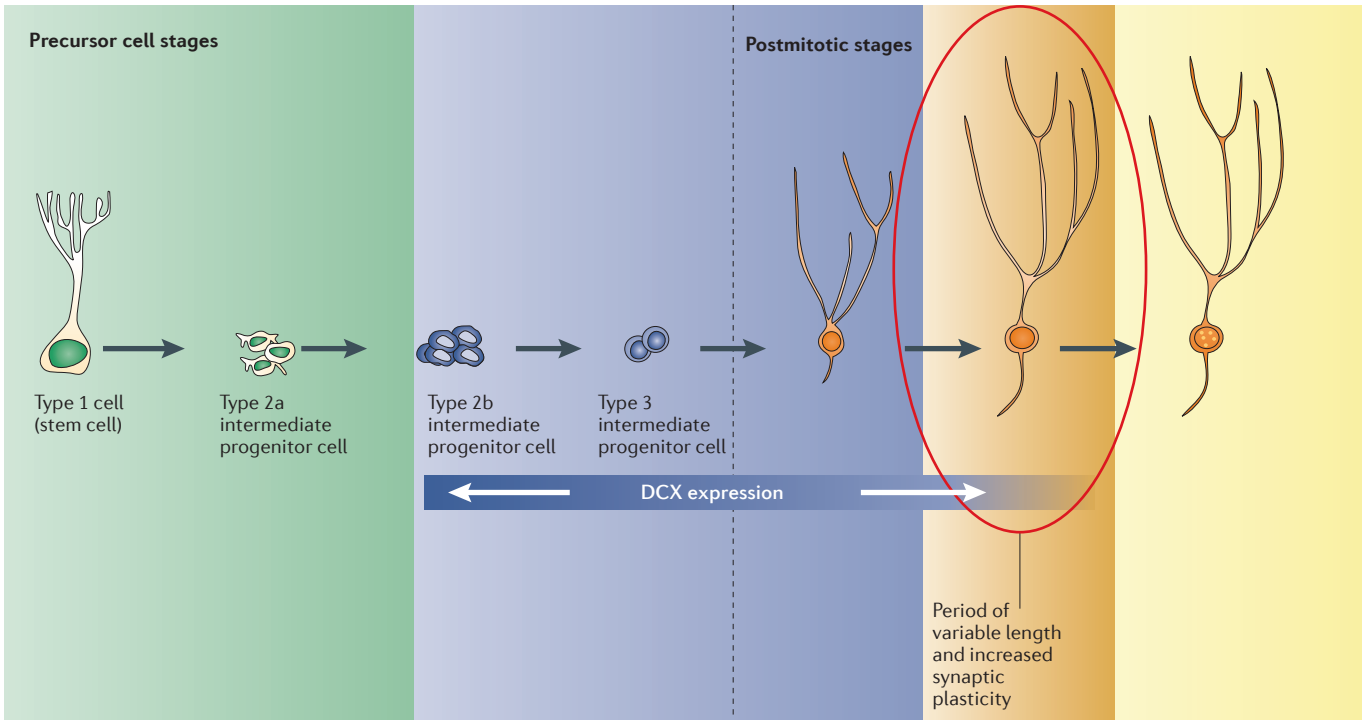

Figure 4 | **The doublecortin stage of adult hippocampal neurogenesis.** Adult hippocampal neurogenesis not only lastingly alters the network of the hippocampus (FIG. 3) but also provides a pool of immature neurons that appear to have a particular functionality. In fact, the new, immature neurons contribute to synaptic plasticity of the dentate gyrus. A surrogate marker for cells at this highly plastic stage is doublecortin (DCX). DCX marks neurons in the presumed 'standby mode' (BOX 3) but is not specific to them. During their development, the new neurons start to express DCX once they have become restricted to the neuronal lineage[91]. DCX acts as a modulator of the cytoskeleton[92], and DCX expression is therefore associated with the highly plastic stages of migration, neuritogenesis and the establishment of functional connections[15,57]. The length of this period of high plasticity appears to vary between species, and it has been proposed that the size of the pool of these highly plastic cells provides an evolutionary advantage in terms of greater adaptability and cognitive flexibility[8,10].

but related effects. The new neurons lastingly alter the network of the dentate gyrus and the mossy fibre tract. However, this functionality is dependent on a preceding phenomenon that occurs during an immature stage of the cells: after neuritic and synaptic connectivity has been established, new neurons go through a well-described 'sensitive period' of increased synaptic plasticity (in the sense that they have a lower threshold for the induction of long-term potentiation)[57–59]. As the network of the dentate gyrus is heavily inhibited by local interneurons, it is the new cells that add synaptic and cellular plasticity at a given time[60]. At this stage, cellular plasticity acts through particular synaptic plasticity. As new neurons are few, this still amounts to very sparse excitation — a hallmark of network activity in the dentate gyrus. At least the first part of the sensitive period during which excitability is increased is characterized by the expression of DCX; however, DCX is already expressed before this critical window opens (FIG. 4).

The red fox has surprisingly large numbers of DCX-expressing cells but shows only very moderate proliferative activity in the dentate gyrus[61]. The authors of this study concluded[61] that in this species, the immature — that is, excitable — phase of adult neurogenesis is particularly long, leading to large numbers of DCX-expressing cells (BOX 3). Foxes are highly flexible in their adaptation to new situations and environments and thus fulfil our criterion of a species that should be high in hippocampal neurogenesis. But 'high' might not have to mean that a large number of new neurons are produced (or that proliferation is high) in absolute terms; it could also refer to the presence of a large number of immature, excitable cells, allowing the dentate gyrus to flexibly respond to environmental and situational demand. Humans might fall into this category as well because in humans, granule cell maturation takes a very long time. On the basis of a large-scale comparative study among 17 mammalian species, Amrein *et al.* developed the hypothesis that species differ most strongly with respect to the amount and dynamics of this 'differentiation' rather than other aspects such as cell proliferation[10].

The number of DCX-expressing cells in the adult and ageing human hippocampus might be low in absolute terms, but it is high compared to the level of cell proliferation[26]. There is probably a mutual dependence between the length of the sensitive period and the number of immature cells, and this is likely to be species-dependent; the same level of plasticity might be obtainable with different combinations of cell numbers and durations of the sensitive period.

New neurons and affective behaviour

Adult hippocampal neurogenesis is also involved in affective behaviour, and this is highly plausible given the fact that the hippocampus is part of the limbic system. An influential hypothesis has proposed that impaired adult neurogenesis has a crucial role in the development and course of major depression[62]. A similar idea has been proposed for schizophrenia[63]. Besides having a direct impact on cognitive symptoms in affective disorders, adult-generated neurons might be crucial for affective functions per se. This might imply that species with a greater level of adult hippocampal neurogenesis are at greater risk of experiencing the consequences of impaired neurogenesis on mood as well. This hypothesis is difficult to prove, as both major

Box 3 | **'Standby' neurons**

The idea that immature neurons serve particular functions and, as a result, prolonged periods of maturation might be useful rather than problematic was first discussed in the context of a population of cells at the central canal of the spinal cord[83]. That study coined the term 'standby mode' for these immature neurons on the basis of their characteristic electrophysiological properties. In different wording, this idea is also central to the hypothesis that species differ most strongly in the duration of the 'immature' period of new neurons rather than other aspects, such as the amount of cell proliferation[10]. Gomez-Climent *et al.*[84] generalized this idea to other populations of immature cells throughout the brain that are, besides by their characteristic electrophysiological features, identifiable by their expression of doublecortin (DCX) and the polysialylated form of the neural cell adhesion molecule PSA-NCAM. At least a subset of these cells, for example, in the piriform cortex, are not adult generated but functionally resemble the immature neurons of the adult hippocampus[85]. A prominent population of such immature cells is found in layer II of the cortex of rodents[84], cats[86] and rhesus monkeys[86], but their neurotransmitter phenotype is not yet entirely clear. The existence of 'standby neurons' might thus not be limited to adult neurogenesis but be more widespread than has been acknowledged so far. Adult neurogenesis would represent a way to provide a sensitive structure with new neurons that enable a particular functionality.

depression and schizophrenia are essentially human diseases for which hardly any good animal models exist. But the link might lie in the fact that major depression and schizophrenia, as well as many types of dementia, are associated with reduced cognitive flexibility[64,65]. Persevering thoughts are typical and patients tend to abhor novelty. Failing adult hippocampal neurogenesis might explain part of the clinical picture. If proven in one form or another, this might be an indication that the proposed increased adaptability through adult hippocampal neurogenesis could come at a price.

Conclusion

The aim of this Opinion article has been to address old questions from a new perspective: what if adult neurogenesis in the dentate gyrus is not an atavism but a late acquisition and specialization, and what if there has been evolution towards adult hippocampal neurogenesis, not away from it?

To bring an ecological perspective to research on adult neurogenesis, more data from wild species have to be collected and be related to the specific but variable demands on hippocampal plasticity that are encountered under real-life conditions outside the laboratory. In their book *Plasticity, Robustness, Development, and Evolution*, Bateson and Gluckman have developed a conceptual framework of how robustness and plasticity in developmental processes are linked beyond an either/or mechanism[13]. Adult hippocampal neurogenesis might represent a particular case of such integration by providing a joint solution to the stability–plasticity dilemma in neuronal networks capable of learning and the robustness–plasticity dilemma of development. To prove this hypothesis will be a considerable challenge. We need, first, the development of a more specific ethological and evolutionary hypothesis of adult neurogenesis than could be provided in this article; second, systematically acquired qualitative and quantitative data on adult neurogenesis in many more species, as well as detailed and quantifiable ethological data to which that information can be related; third, deeper insight into the functional benefits provided by adult hippocampal neurogenesis, by incorporating the current systems level perspective with an ethological one; and last, comprehensive mathematical and computational models as tools to understand scenarios of adaptation that are potentially supported by adult neurogenesis. For the latter, a first promising example has been published, in a paper in which putative neurogenesis-dependent tasks were applied to human subjects with depression, for whom the theory would predict impaired adult neurogenesis[66].

Allowing, even if only for the sake of argument, this new viewpoint might fundamentally alter the way we study adult neurogenesis, how we justify our research and what might ultimately result from it. We should dare to embrace the idea that adult neurogenesis is a trait that is central to humanity rather than an outdated heritage from our evolutionary past.

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