The neurogenic reserve hypothesis: what is adult hippocampal neurogenesis good for?

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The neurogenic reserve hypothesis: what is adult hippocampal neurogenesis good for?

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ABSTRACT | Several theories have proposed possible functions of adult neurogenesis in learning processes on a systems level, such as the avoidance of catastrophic interference and the encoding of temporal and contextual information, and in emotional behavior. Under the assumption of such functionality of new neurons, the question arises: what are the consequences of adult hippocampal neurogenesis beyond the temporally immediate computational benefit? What might provide the evolutionary advantage of maintaining neurogenesis in the dentate gyrus but almost nowhere else? I propose that over the course of life, activity-dependently regulated adult neurogenesis reveals its true significance in the retained ability for lasting and cumulative network adaptations. The hippocampal precursor cells that generate new neurons with their particular acute function represent a 'neurogenic reserve': the potential to remain flexible and plastic in hippocampal learning when the individual is exposed to novelty and complexity.

Introduction

The 'neurogenic reserve' hypothesis, proposed here, intends to explain how neurogenesis in the adult hippocampus might contribute to the maintenance and promotion of hippocampal function in health and disease across the lifespan. The theory makes explicit reference to the neural reserve theory, first proposed by R. Katzman and P. Satz and elaborated, for example, by Y. Stern [1,2,3,4]. A 'neural reserve' is sought as explanation, for example, for the observation that in cases of neurodegenerative disease, the amount of neuropathological damage shows no tight correlation with the functional impairment [5]. Apparently healthy subjects might die with a brain full of Alzheimer-like plaques, although modest plaque load in other individuals might already be associated with massive dementia [6]. The neural reserve would represent the brain's compensatory potential in the face of neurodegeneration. This reserve is thought to lie in 'brain networks or cognitive paradigms that are less susceptible to disruption, perhaps [because] they are more efficient or have greater capacity' [7]. The neurogenic reserve theory specifies that in the hippocampus, adult neurogenesis might activity- and experience-dependently produce a potential for sustained cellular plasticity with increasing age but from childhood onward, thereby providing such greater capacity and efficiency. The particular relevance of this special case of a reserve derives from the prominent role of the hippocampus in higher cognition, most notably learning and memory and emotional behavior. In animal experiments, both physical and cognitive 'activity' reduced the age-dependent decline in precursor cell proliferation in the dentate gyrus [8,9,10]. Sustained exposure to a complex environment, even if started only in midlife, maintained neurogenesis at a higher level and also resulted in improved learning performance [9]. Thereby, adult neurogenesis might contribute to the well-known but poorly understood observation that activity – in the sense of leading an active life – is 'good for the brain' and promotes successful aging.

The local restriction of adult neurogenesis as key to ist function

Adult neurogenesis, the lifelong generation of new neurons in the adult hippocampus and olfactory system, captures the scientific and public imagination with its seemingly obvious implications for regenerative medicine. This fascination is contrasted by an intriguing insecurity about what the new neurons are actually good for, although some agreement has been reached that they are involved in learning [11,12,13,14,15,16]. However, the fact that adult neurogenesis is regulated by activity and is thereby intricately linked to brain function has served as a strong argument against its dismissal as a mere atavism. Increasingly, specific ideas about the functional contribution of adult neurogenesis in the hippocampus are proposed [17,18,19]. Several studies suggest a possible role in the encoding of contextual information [20,21,22]. Given that synaptic plasticity as the main type of structural change related to 'function' is available at much lower costs than afforded by the lifelong maintenance of neurogenesis, the functional contribution of the new neurons must be unique and worth this exceptional effort. The places where neurogenesis occurs must be substantially different from the rest of the brain in that they require a type of plasticity that is dispensable or even damaging

elsewhere. The olfactory system, the only other site of adult neurogenesis besides the hippocampus, is not further considered here, but theories on the functional relevance of adult olfactory neurogenesis exist [23]. One hippocampal particularity lies in a structural bottleneck in the neuronal network, which is exactly the position at which adult neurogenesis occurs. New neurons are added only to the granule cell layer of the dentate gyrus, the relatively narrow input structure to the hippocampus proper, a structure centrally involved in learning and memory processes. Strictly speaking, the bottleneck lies in the mossy fiber projection of the dentate gyrus into the much smaller region CA3 [24]. Between the entorhinal cortex and the dentate gyrus even a divergence to greater cell numbers occurs. However, representations and activity patterns in the dentate gyrus are extremely sparse, so that divergence of the input, sparseness of the firing rate and the funneled output to CA3 come together to constitute the bottleneck. The new neurons contribute to the mossy fiber tract and thereby structurally counteract the narrowness of this spot.

Possible functions of adult hippocampal neurogenesis on the systems level

Our assumption is that for some reason, the mossy fiber connection has to be as lean as possible but as strong as necessary [12]. Adding new neurons to this reduced network with its sparsely firing neurons might be a way to economically optimize the projection into the hippocampus proper. Adding new neurons here might be a way to solve the so-called stability–plasticity dilemma, which is particularly pressing at a network position where constantly new information is flooding in and endangers the proper consolidation of the previously learned contents [19].

Along a different line of reasoning, Aimone and colleagues have proposed that new neurons might increase the overlap between temporally related patterns [18]. Because of an increased sensitivity of immature cells [25,26,27], they would be more likely to fire together in both situations. Over time, this association disappears (as new young neurons with increased sensitivity appear), so that two events that have a close temporal association will result in greater pattern overlap than two events that are separated by larger time intervals. Aimone's theory thus states that 'an overlap in dentate gyrus sparse codes initiates…temporal associations in the hippocampus during early stages of memory formation' [18].

These two ideas actually do not exclude each other. Rather, the issue of temporal resolution might help to define to which cognitive features the 'increased sensitivity' actually relates. Several additional hypotheses have been proposed, among others by Becker [28], Snyder *et al.* [29], Deisseroth *et al.* [30] and Gould *et al.* [11]. All of these network models share a relative emphasis on memory storage rather than processing (or learning), and often do not yet offer a satisfactory explanation why the problem might not be solvable at lower cost with the help of synaptic plasticity [31]. Several lines of reasoning focus on the particularity that the new neurons have a lower threshold for the induction of long-term potentiation than older cells, often leading to concepts that favor a transient function of the new cells [32,33].

This still somewhat blurred picture might be as far as we can get in elucidating the functional relevance of adult neurogenesis with the presently available methods. However, the discussed scenarios suggest that true experimental progress in this matter will not so much come from sophisticated tools to suppress or modulate neurogenesis without confounding side effects (as assumed by many and as important as this will be) but more from new or substantially refined behavioral tests that allow measurement of exactly those hippocampal functions for which adult neurogenesis is required.

There is a second line of evidence for a contribution of adult neurogenesis to hippocampal function with respect to affective behavior. Rene Hen and his colleagues argue that adult neurogenesis in the dentate gyrus might be strongly involved in emotion, at least in the context of depression and its treatment [34]. Eliminating adult neurogenesis in C57BL/6 mice by irradiation prevented anxiety from being treated with antidepressants [35]. Interestingly, this relationship was not apparent in another strain of mice, Balb/c [36], emphasizing the large impact of genetic variation on traits associated with adult neurogenesis [37]. In the present context, we focus on a possible role of adult neurogenesis in learning and memory while acknowledging the fact that an as yet unresolved relationship exists between the putative involvement of adult neurogenesis in learning and emotional behavior.

Functional relevance beyond the systems level and on longer timescales

The fact that 'activity' is an appropriate stimulus for adult neurogenesis adds another, temporal dimension to the question of what new neurons are good for. Activity-dependent regulation of

adult neurogenesis shows an intriguing duality: the acute recruitment of the currently available immature cell (which is in its critical time window for activity-dependent recruitment) and the stimulation of mechanisms that increase the pool of such recruitable cells on longer timescales. In the course of neuronal development in the adult hippocampus, the decision for new neurons to die or to become integrated into the network is made very early, long before functional integration. The main survival effect appears stochastic and driven by overall activity levels. Excitatory GABAergic input has been identified as one mechanism that promotes maturation of newly generated cells [38,39] but others might play a role, including the effects of neurotrophic factors (most notably BDNF) and other transmitter systems (above all the serotonergic system). There seems to be a second, late survival effect, which is actually dependent on the full functional integration of the new neuron, but for the quantity of survival promotion it plays a smaller role and very little is known about such fine-tuning regulation [40].

Increasing adult neurogenesis by environmental enrichment has been consistently associated with improvement in learning tasks, but adult neurogenesis cannot be made responsible for all functional changes associated with environmental enrichment. Abolishing adult neurogenesis by irradiation did not lead to the disappearance of functional benefits from environmental enrichment – at least within the scope of the tests that were applied in that study [41]. Although the study does not disprove that enrichment might exert functional effects by increasing adult neurogenesis, it reminds us that correlation is not causality.

A need for increased temporal resolution as in Aimone's theory might exactly arise from the experienced complexity of a given situation and represent the specific trigger first to recruit a new neuron, second to eliminate unwanted new neurons and third to increase precursor cell proliferation [42,43]. Learning of contexts and locomotion might be inseparable, because for an animal in real life they hardly ever occur alone. For animals (and especially rodents, in which most of the research on adult neurogenesis has been done), cognition, as long as it is related to the outer world, is largely inseparable from locomotion within that world. There are of course other aspects of cognition that might be independent of locomotion, but movement in the physical space and the cognitive space are tightly linked. The often-criticized bias in hippocampus research on spatial memory might thus actually be not as wrong as sometimes assumed – especially if the principles of spatial memory are developed into concepts of a 'space for memory' [44,45]. The two issues are not the same, however: the test bias for spatial navigation and the fact that mice usually have to physically move through their environment for learning of the outer world to occur are distinct phenomena.

A synthesis of nonspecific and specific regulatory mechanisms

In the laboratory, we can separate physical and cognitive activity for mice to a certain degree. Both physical exercise and exposure to complex environments or learning stimuli increase adult neurogenesis [43,46,47,48,49]. However, whereas physical activity acts on proliferating precursor cells and induces their division, the more cognitive stimuli rather promote the survival of newborn postmitotic cells [47,48]. These experiments have led us to the hypothesis that the activity-dependent regulation of adult neurogenesis consists of a nonspecific regulation of precursor cell proliferation (exemplified by physical activity) and specific learning stimuli that recruit the newborn cells. This distinction, which is useful from an experimental perspective, might actually be somewhat misleading. In fact, we have found that not only does the acute stimulus of physical exercise wear off after a few days but the prolonged stimulation by exercise at the same time also maintains precursor cell proliferation and counteracts the physiological age-related decline of adult neurogenesis [10]. Sustained cognitive challenges as well as sustained physical exercise thus maintain the pool of new neurons that might be recruited if the need arises in a situation of cognitive complexity. Activity thus results in a plastic adaptation that is an investment for the future.

This idea solves the puzzle of why exercise should have any cognitive consequences at all. Physical activity, especially over longer periods of time, might indicate to the brain an increased chance of experiencing exactly those situations rich in complexity and novelty that presumably benefit from more new neurons. We thus propose that (literally) in the long run it is not isolated physical activity that is good for the brain, but physical activity in the context of cognitive challenges. Feedback from systems involved in locomotion might serve as a means of communication between the periphery and processes involved in brain plasticity. Mechanistically, different aspects of 'activity,' physical versus cognitive, have distinguishable nonspecific versus specific effects. However, the overall principle is that adult neurogenesis responds to the need for locomotion as an indicator of cognitive challenge. So locomotion is a nonspecific trigger related to specific cognitive events. The advantage of these

mechanisms is that a rather broadly activated system sets the stage on which the particular cognitive stimuli that recruit individual neurons might act. The key idea of the neurogenic reserve hypothesis is that this mechanism acts on both short and very long timescales. Short-term events prepare for long-term levels of plasticity. This might also explain the surprising finding that the upregulating effects of physical activity on neurogenesis are transmissible from the physically active mother to her unborn offspring [50]. All of these events would obviously take place within the larger context of synaptic plasticity. Walking also facilitates long-term potentiation in rats [51].

Within this model, it also becomes clear why adult neurogenesis might be functionally beneficial although it decreases to very low levels with increasing age (►Fig. 1). Even the first report on adult hippocampal neurogenesis noted this steep decline to very low numbers of newborn neurons throughout the remaining lifetime [52]. Most importantly, however, despite its costs, adult neurogenesis never seems to cease completely. Even in the oldest rodent or human subjects investigated, low levels of adult hippocampal neurogenesis have been detected. Whereas the number of new neurons that is produced early in life might lead to a measurable increase in the size of the dentate gyrus [53,54], the contribution of adult neurogenesis appears to be qualitative rather than quantitative for the rest of life. Any proposed function that would require as many new neurons in an old as in a young animal is thus not compatible with the hippocampal reality. Old animals have already experienced more and consequently need less acute adaptation. However, exploration of novel and complex environments even in old mice robustly induced adult neurogenesis by promoting the survival of newly generated immature neurons [55]. In old age this effect was even relatively larger than in younger animals, suggesting that, if challenged, the aged hippocampus attempts to mobilize its entire potential of cellular plasticity. Thus, although most 'adult' neurogenesis actually appears to take place in youth and early adulthood and is minute for the remaining lifespan, its cumulative nature and its effects on very long timescales imply functional benefits that do not correlate with the number of new neurons at the given time. Importantly, the low level is reached well within the reproductive period, so that a mechanism based on a neurogenic reserve residing in low levels of neurogenesis would not escape evolutionary pressure.

The cellular representation of the neurogenic reserve in the adult hippocampus

The very low levels of adult neurogenesis, together with its local restriction to the hippocampus and just one other neurogenic region in the olfactory system, its limitation to only one type of new hippocampal neuron and the tight link to hippocampal function have come as a disappointment to those who hoped that adult neurogenesis might serve as a source for restoring cellular losses. In many models of pathology, adult neurogenesis is robustly induced but this effect seems to be transient and nonspecific [56].

On the physiological side, such nonspecific regulation is found in the well-known response of adult hippocampal neurogenesis to physical activity [49]. Nonspecific stimuli exert a pro-proliferative effect on the precursor cells from which adult neurogenesis originates [48]. The hypothesis is that this increase provides a potential represented by the proliferating precursor cells in the dentate gyrus, from which, in cases of computational need, new neurons can be recruited and integrated into the network. These still would be relatively nonspecific and be based on GABAergic signaling rather than specific glutamatergic input (which would be appropriate for the content-bearing input from the entorhinal cortex). The activated GABA system might represent the mediator of activity on the cellular level that is responsible for promoting neurogenesis from proliferative precursor cells [38,39,57]. The GABA-based regulation is likely to be complemented by other mechanisms, such as via neurotrophic factors or other neurotransmitters. The mechanism that underlies the increased proliferation of type 2 progenitor cells, the cell type in the course of adult neurogenesis with the highest proliferative activity, remains to be identified. Circulating factors have been proposed but a mechanism based on transmitter signaling might be more appropriate in light of the present hypothesis. Serotonin is a likely candidate [58]. In any case, the realized potential for adult neurogenesis would represent an event-triggered investment for the future and prepare the hippocampal network for coming situations that are similar to the one that has now induced the integration of the new neuron. The precursor cells that are and remain in the cell cycle would represent the structural correlate of the neurogenic reserve. Nora Abrous and colleagues have demonstrated how learning alters the course of adult hippocampal neurogenesis by affecting proliferating precursor cells, selective survival of new neurons and specific elimination of other immature cells,

thereby suggesting how neurogenesis contributes to the formation of adapted networks [42].

Testing the neurogenic reserve hypothesis

The neurogenic reserve hypothesis aims at providing an explanation of why activity-dependently controlled adult neurogenesis might be beneficial over long periods of time. The emphasis is on the fact that adult neurogenesis is regulated by activity, and functional consequences might become particularly apparent over long timescales. The hypothesis relies on certain assumptions about the functional contribution new neurons might make to a network (as outlined above and e.g. in Ref. [19]), but with slight modifications the idea should be adjustable to many concepts of how individual new neurons might contribute to hippocampal function.

To test the hypothesis, one will first have to prove that an increased potential for adult neurogenesis that is evoked by sustained activity and enrichment indeed allows the recruitment of relatively more new neurons in new challenging situations and that this increase leads to additional functional improvement. ►Fig. 1 indicates how one might challenge animals with sequences of 'environments' after different levels of pre-exposure to other environments and – ideally – a targeted manipulation of adult neurogenesis.

Because an interaction effect is studied this experiment is difficult, and not only because many animals are needed to achieve the necessary power. The other critical issue is the choice of the behavioral test. Adequate modifications of available tests will be needed to allow retesting over long time intervals and relate incremental changes in test performance to underlying variation in adult neurogenesis. Testing the neurogenic reserve hypothesis might also mean turning to ethologically more relevant tests than most paradigms used in the laboratory [59]. Especially with regard to longitudinal assessment of traits, the rodent literature is scarce. A few aspects, however, can be tested in a straightforward way: if the neurogenic reserve hypothesis is true, one will, for example, also find that in an old animal that has seen very many environments, the regulatory effect of yet another new environment on adult neurogenesis will be lower than in a naïve animal. The relationship between adult neurogenesis and levels of adult neurogenesis might consequently become complicated: it is conceivable that despite a positive correlation between adult neurogenesis and cognitive performance on certain hippocampus-dependent functional domains, exceptionally well-adapted animals might even have less adult neurogenesis than those for which there are still challenges.

Medical implications of a neurogenic reserve

If we extrapolate the animal data to the situation in humans, broad ranges of activity early in life would not only help to build a highly optimized hippocampal network adapted to a complex life, lifelong activity would also contribute to a neurogenic reserve by keeping precursor cells in cycle and thereby generating an incessant stream of immature, potentially recruitable neurons [10]. Adult neurogenesis might thus be able to contribute to primary and secondary prevention of failing cognitive functions related to the hippocampus rather than to the replacement of neuronal loss. The main function of adult neurogenesis does not seem to lie in regeneration, and the neurogenic reserve hypothesis does not primarily imply that high levels of neurogenesis would allow better regeneration. Still, regeneration-like responses might exist and have, for example, been reported for adult neurogenesis in models of Alzheimer's disease [60].

Adjusting the activity side will be only one part of the equation, but one whose modulation is in the hands of the individual. Doing what one can to optimize activity-dependent plasticity by building a neurogenic reserve is no foolproof and invariant way to successful aging [61]. However, the concept might encourage people to take charge of that part that they can influence and reveals how a reserve might be rooted in a cellular level.

Concluding remarks

The neurogenic reserve hypothesis aims at explaining how the activity-dependent incorporation of a low number of neurons into the hippocampal network can lead to a functional benefit along the course of life of an individual. The core idea is that 'activity' preserves the potential for cell-based plasticity by maintaining adult neurogenesis in an activated state. To test the hypothesis, experiments following and manipulating adult neurogenesis across the lifespan while measuring an animal's fitness and adaptability to its changing environment will be needed.

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References

1. P. Satz, Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory, *Neuropsychology* **7** (1993), pp. 273–295.
2. R. Katzman, Education and the prevalence of dementia and Alzheimer's disease, *Neurology* **43** (1993), pp. 13–20.
3. N. Scarmeas and Y. Stern, Cognitive reserve and lifestyle, *J. Clin. Exp. Neuropsychol.* **25** (2003), pp. 625–633.
4. Y. Stern *et al.*, Exploring the neural basis of cognitive reserve, *J. Clin. Exp. Neuropsychol.* **25** (2003), pp. 691–701.
5. L. Fratiglioni *et al.*, An active and socially integrated lifestyle in late life might protect against dementia, *Lancet Neurol.* **3** (2004), pp. 343–353.
6. R. Katzman *et al.*, Development of dementing illnesses in an 80-year-old volunteer cohort, *Ann. Neurol.* **25** (1989), pp. 317–324.
7. Y. Stern, Cognitive reserve and Alzheimer disease, *Alzheimer Dis. Assoc. Disord.* **20** (2006), pp. 112–117.
8. G. Kempermann and F.H. Gage, Experience-dependent regulation of adult hippocampal neurogenesis: effects of long-term stimulation and stimulus withdrawal, *Hippocampus* **9** (1999), pp. 321–332.
9. G. Kempermann *et al.*, Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment, *Ann. Neurol.* **52** (2002), pp. 135–143.
10. G. Kronenberg *et al.*, Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus, *Neurobiol. Aging* **27** (2006), pp. 1505–1513.
11. E. Gould *et al.*, Neurogenesis in adulthood: a possible role in learning, *Trends Cogn. Sci.* **3** (1999), pp. 186–192.
12. G. Kempermann, Why new neurons? Possible functions for adult hippocampal neurogenesis, *J. Neurosci.* **22** (2002), pp. 635–638.
13. A.F. Schinder and F.H. Gage, A hypothesis about the role of adult neurogenesis in hippocampal function, *Physiology (Bethesda)* **19** (2004), pp. 253–261.
14. E. Bruel-Jungerman *et al.*, Adult hippocampal neurogenesis, synaptic plasticity and memory: facts and hypotheses, *Rev. Neurosci.* **18** (2007), pp. 93–114.
15. Y. Kitabatake *et al.*, Adult neurogenesis and hippocampal memory function: new cells, more plasticity, new memories?, *Neurosurg. Clin. N. Am.* **18** (2007), pp. 105–113.
16. F. Nottebohm, Neuronal replacement in adult brain, *Brain Res. Bull.* **57** (2002), pp. 737–749.
17. S. Becker and J.M. Wojtowicz, A model of hippocampal neurogenesis in memory and mood disorders, *Trends Cogn. Sci.* **11** (2007), pp. 70–76.
18. J.B. Aimone *et al.*, Potential role for adult neurogenesis in the encoding of time in new memories, *Nat. Neurosci.* **9** (2006), pp. 723–727.
19. L. Wiskott *et al.*, A functional hypothesis for adult hippocampal neurogenesis: avoidance of catastrophic interference in the dentate gyrus, *Hippocampus* **16** (2006), pp. 329–343.
20. M.D. Saxe *et al.*, Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus, *Proc. Natl. Acad. Sci. U. S. A.* **103** (2006), pp. 17501–17506.
21. T.J. Shors *et al.*, Neurogenesis may relate to some but not all types of hippocampal-dependent learning, *Hippocampus* **12** (2002), pp. 578–584.
22. K. Jaako-Movits *et al.*, Developmental lead exposure impairs contextual fear conditioning and reduces adult hippocampal neurogenesis in the rat brain, *Int. J. Dev. Neurosci.* **23** (2005), pp. 627–635.
23. P.M. Lledo and A. Saghatelyan, Integrating new neurons into the adult olfactory bulb: joining the network, life-death decisions, and the effects of sensory experience, *Trends Neurosci.* **28** (2005), pp. 248–254.
24. A. Treves and E.T. Rolls, Computational analysis of the role of the hippocampus in memory, *Hippocampus* **4** (1994), pp. 374–391.
25. C. Schmidt-Hieber *et al.*, Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus, *Nature* **429** (2004), pp. 184–187.
26. S. Wang *et al.*, Heterogenous properties of dentate granule neurons in the adult rat, *J. Neurobiol.* **42** (2000), pp. 248–257.
27. S. Ge *et al.*, A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain, *Neuron* **54** (2007), pp. 559–566.
28. S. Becker, A computational principle for hippocampal learning and neurogenesis, *Hippocampus* **15** (2005), pp. 722–738.

29. J.S. Snyder *et al.*, A role for adult neurogenesis in spatial long-term memory, *Neuroscience* **130** (2005), pp. 843–852.

30. K. Deisseroth *et al.*, Excitation-neurogenesis coupling in adult neural stem/progenitor cells, *Neuron* **42** (2004), pp. 535–552.

31. G. Kempermann *et al.*, Functional significance of adult neurogenesis, *Curr. Opin. Neurobiol.* **14** (2004), pp. 186–191.

32. F. Doetsch and R. Hen, Young and excitable: the function of new neurons in the adult mammalian brain, *Curr. Opin. Neurobiol.* **15** (2005), pp. 121–128.

33. J. Bischofberger, Young and excitable: new neurons in memory networks, *Nat. Neurosci.* **10** (2007), pp. 273–275.

34. A. Sahay and R. Hen, Adult hippocampal neurogenesis in depression, *Nat. Neurosci.* **10** (2007), pp. 1110–1115.

35. L. Santarelli *et al.*, Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants, *Science* **301** (2003), pp. 805–809.

36. K.A. Holick *et al.*, Behavioral effects of chronic fluoxetine in BALB/cJ mice do not require adult hippocampal neurogenesis or the serotonin 1A receptor, *Neuropsychopharmacology* **33** (2008), pp. 406–417.

37. G. Kempermann *et al.*, Natural variation and genetic covariance in adult hippocampal neurogenesis, *Proc. Natl. Acad. Sci. U. S. A.* **103** (2006), pp. 780–785.

38. S. Ge *et al.*, GABA regulates synaptic integration of newly generated neurons in the adult brain, *Nature* **439** (2006), pp. 589–593.

39. Y. Tozuka *et al.*, GABAergic excitation promotes neuronal differentiation in adult hippocampal progenitor cells, *Neuron* **47** (2005), pp. 803–815.

40. H. Song *et al.*, New neurons in the adult mammalian brain: synaptogenesis and functional integration, *J. Neurosci.* **25** (2005), pp. 10366–10368.

41. D. Meshi *et al.*, Hippocampal neurogenesis is not required for behavioral effects of environmental enrichment, *Nat. Neurosci.* **9** (2006), pp. 729–731.

42. D. Dupret *et al.*, Spatial learning depends on both the addition and removal of new hippocampal neurons, *PLoS Biol.* **5** (2007), p. e214.

43. M.D. Dobrossy *et al.*, Differential effects of learning on neurogenesis: learning increases or decreases the number of newly born cells depending on their birth date, *Mol. Psychiatry* **8** (2003), pp. 974–982.

44. H. Eichenbaum, Is the rodent hippocampus just for 'place'?, *Curr. Opin. Neurobiol.* **6** (1996), pp. 187–195.

45. H. Eichenbaum *et al.*, The hippocampus, memory, and place cells: is it spatial memory or a memory space?, *Neuron* **23** (1999), pp. 209–226.

46. E. Gould *et al.*, Learning enhances adult neurogenesis in the hippocampal formation, *Nat. Neurosci.* **2** (1999), pp. 260–265.

47. G. Kempermann *et al.*, More hippocampal neurons in adult mice living in an enriched environment, *Nature* **386** (1997), pp. 493–495.

48. G. Kronenberg *et al.*, Subpopulations of proliferating cells of the adult hippocampus respond differently to physiologic neurogenic stimuli, *J. Comp. Neurol.* **467** (2003), pp. 455–463.

49. H. van Praag *et al.*, Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus, *Nat. Neurosci.* **2** (1999), pp. 266–270.

50. A. Bick-Sander *et al.*, Running in pregnancy transiently increases postnatal hippocampal neurogenesis in the offspring, *Proc. Natl. Acad. Sci. U. S. A.* **103** (2006), pp. 3852–3857.

51. L.S. Leung *et al.*, Cholinergic activity enhances hippocampal long-term potentiation in CA1 during walking in rats, *J. Neurosci.* **23** (2003), pp. 9297–9304.

52. J. Altman and G.D. Das, Autoradiographic and histologic evidence of postnatal neurogenesis in rats, *J. Comp. Neurol.* **124** (1965), pp. 319–335.

53. S.A. Bayer, Neuron production in the hippocampus and olfactory bulb of the adult rat brain: addition or replacement?, *Ann. N. Y. Acad. Sci.* **457** (1985), pp. 163–172.

54. D. Crespo *et al.*, Evidence that late-generated granule cells do not simply replace earlier formed neurons in the rat dentate gyrus, *Exp. Brain Res.* **62** (1986), pp. 541–548.

55. G. Kempermann *et al.*, Experience-induced neurogenesis in the senescent dentate gyrus, *J. Neurosci.* **18** (1998), pp. 3206–3212.

56. J. Dietrich and G. Kempermann, Role of endogenous neural stem cells in neurological disease and brain repair, *Adv. Exp. Med. Biol.* **557** (2006), pp. 191–220.

57. L.P. Wang *et al.*, A subpopulation of precursor cells in the mouse dentate gyrus receives synaptic GABAergic input, *Mol. Cell. Neurosci.* **29** (2005), pp. 181–189.

58. J.M. Encinas *et al.*, Fluoxetine targets early progenitor cells in the adult brain, *Proc. Natl. Acad. Sci. U. S. A.* **103** (2006), pp. 8233–8238.

59. I. Branchi and L. Ricceri, Refining learning and memory assessment in laboratory rodents. An ethological perspective, *Ann. Ist. Super. Sanita* **40** (2004), pp. 231–236.

60. K. Jin *et al.*, Enhanced neurogenesis in Alzheimer's disease transgenic (PDGF-APPSw,Ind) mice, *Proc. Natl. Acad. Sci. U. S. A.* **101** (2004), pp. 13363–13367.

61. U. Lindenberger *et al.*, Delineating brain-behavior mappings across the lifespan: substantive and methodological advances in developmental neuroscience, *Neurosci. Biobehav. Rev.* **30** (2006), pp. 713–717.

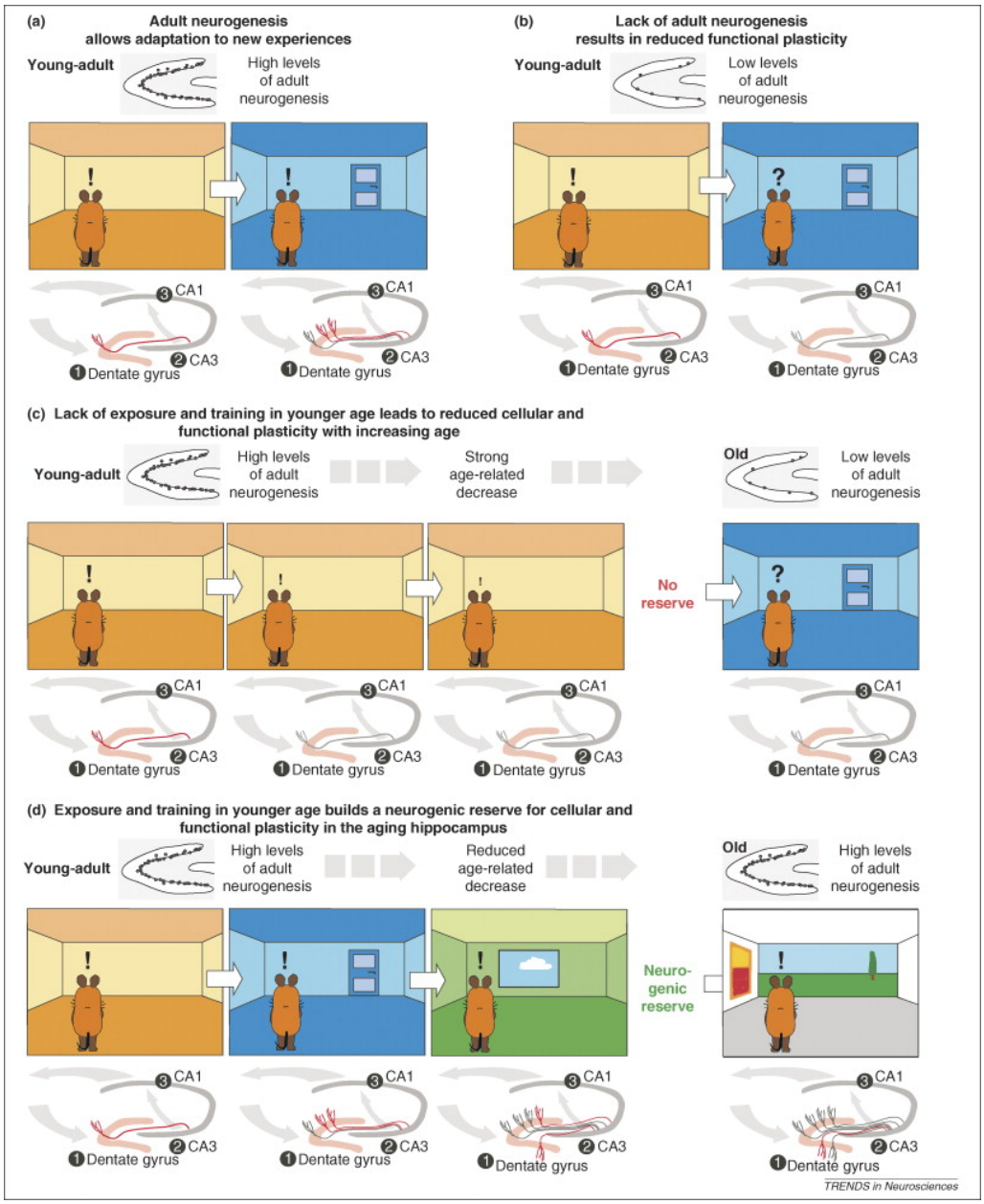

Fig.1. The neurogenic reserve hypothesis. (a) The key idea is that adult neurogenesis allows an adaptation of the hippocampal network to new experiences. With a high level of adult hippocampal neurogenesis (as commonly observed in young age), the mouse that is confronted with a new situation (right panel) that is similar to but distinct from a previously learned situation (left panel) can easily adapt to the new situation and learn the distinguishing differences, thereby expanding its cognitive map (i.e. the representation of the environment) without catastrophic interference between novel and previously learned information [19]. (b) If adult hippocampal neurogenesis is low, this adjustment and optimization of the mossy fiber connection is not possible. Novel information interferes with previously learned information. (c) On longer timescales, the fact comes into play that the learning experience itself (as well as locomotion) as the means of navigation in the physical (and thus cognitive) space affects the regulation of adult neurogenesis. If there is a lack of stimuli, represented by the prolonged exposure to the same environment, adult neurogenesis decreases and the potential for recruiting the necessary new neurons in times of computational need is reduced. No reserve has been built. (d) By contrast, if the individual experiences a high level of complexity and novelty (i.e. has to physically navigate in a complex and changing world), precursor cell activity remains high, a neurogenic reserve is built and the hippocampus can still plastically adopt to very novel situations that are experienced for the first time in older age. 'Die Maus' appears with kind permission of copyright holder Westdeutscher Rundfunk Köln. © I. Schmitt-Menzel/WDR mediagroup licensing GmbH/Die Sendung mit der Maus ® WDR.