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Adult neurogenesis beyond the niche: its potential for driving brain plasticity

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Adult neurogenesis emerges as a tremendous form of plasticity with the continuous addition and loss of neurons in the adult brain. It is unclear how preexisting adult circuits generated during development are capable of modifying existing connections to accommodate the thousands of new synapses formed and exchanged each day. Here we first make parallels with sensory deprivation studies and its ability to induce preexisting non-neurogenic adult circuits to undergo massive reorganization. We then review recent studies that show high structural and synaptic plasticity in circuits directly connected to adult-born neurons. Finally, we propose future directions in the field to decipher how host circuits can accommodate new neuron integration and to determine the impact of adult neurogenesis on global brain plasticity.

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Introduction

Adult neurogenesis, the formation and integration of new neurons in the adult brain, has been established in the last decades to be prevalent in mammals, including humans [1]. Resident stem cells in the hippocampus and subventricular zone produce intermediate progenitors that mainly differentiate into hippocampal granule cell neurons of the dentate gyrus, and into granule and periglomerular neurons of the olfactory bulb.

Neurogenesis was initially thought to be confined to the prenatal period of development, as first presented by Santiago Ramón y Cajal [2]. This conclusion was understandable due to the lack of proliferation markers in the early 20th century, and it also supported static memory theories, which could potentially be disrupted by neurogenesis [3]. In the 1960s proliferating cells were first discovered in the adult brain, which were later confirmed to be neurons, and in 1998, adult-born neurons were discovered in the human hippocampus [4–6]. What these and ensuing studies revealed was not only that continuous addition and turnover of neurons occurs throughout life in defined brain regions, but, as a focus of this review, that pre-existing adult non-neurogenic circuits have the remarkable capacity to adjust to the never-ending flow of newcomers, leading to an endogenous system of major presynaptic and postsynaptic addition and remodeling.

Triggering robust plasticity in the adult brain

Learning and memory in the adult brain requires changes in synaptic connectivity between neurons to encode and store new memories while erasing selected traces of past events and experiences [7]. Predominant forms of synaptic changes include activity-dependent potentiation and/or depression of synaptic strength either first, by presynaptic changes in neurotransmitter release, or by insertion (or removal) of postsynaptic receptors [8]. Receptor insertion can also activate (or silencing) silent synapses, or conversely, receptor removal to make a synapse silent.

Another predominant form of synaptic change is structural plasticity, which is a physical mechanism of remodeling connectivity between neurons, with formation, displacement or elimination of dendritic spines and axonal boutons, including overall structural changes in axonal and dendritic structure, and plays a dominant role during development for establishing proper neuronal connections within the circuit [8,9]. Throughout this review we will refer to structural plasticity as this grand or 'binary' change in structural connectivity and will not discuss more subtle modifications that may affect spine morphology or head size. Structural plasticity provides a large potential for network remodeling because it is not restricted to predefined synaptic sites (such as silent synapses). It was initially believed that structural plasticity was confined to the early postnatal critical period and was absent or rare in the adult brain [10]. Its functional implications in the adult brain constitute an ongoing theoretical and experimental focus of study [11].

A pioneering study in adult monkeys showed that when a digit was amputated, the brain's receptive field of the

amputated digit de-afferented, gradually becoming more responsive to sensory stimulation of neighboring fingers [12]. It was unclear if there was broadly overlapping cortical innervation of all the digits and neurons 'filtered' inputs to define cortical receptive fields or, instead, cortical receptive fields were defined by restricted innervation to discrete regions and sensory deprivation elicited a structural reorganization of sensory inputs, spreading their axons into the deprived region.

A decade later, this second mechanism of axonal sprouting was shown to be the dominant mechanism in striate cortex, where retinal lesions induced sprouting of long-range projecting neurons, suggesting the adult brain to have structural plasticity 'in reserve' until required for remapping after injury or deprivation [13]. In temporal lobe epilepsy, extensive sprouting of dentate granule cell mossy fiber projections into the inner molecular layer occurred [14]. These studies showed that adult brain regions have an enhanced capacity for structural plasticity 'in reserve'(a latent pool), which can be unmasked with disease or specific manipulations. Yet, its role in the healthy adult brain remained unclear.

The development of *in vivo* 2-photon imaging in the brain [15] allowed for measuring structural changes in the same individual neurons tracked over multiple days, which would be impossible with histological methods. Imaging various regions of the neocortex showed that pyramidal neuron spines turnover throughout life, although at a very low level as compared to the critical period of cortical development [16••,17]. When competition between active and inactive adult cortical regions was experimentally established in visual cortex with focal retinal lesions, structural plasticity was enhanced to levels three times higher than control, whereas uniform depletion, which caused no competition between regions, resulted in less spine turnover [18].

Plasticity has been also demonstrated by introducing red photoreceptors into the mouse genome, which are normally dichromatic, making the brain capable of processing new sensory information that was never experienced before [19]. The fact that transgenic mice could now discriminate red color in a behavioral task revealed a remarkable capacity of the brain to take advantage of a new type of sensory input.

Taken together, these studies demonstrated structural plasticity in the adult brain and showed a role for competition in driving this plasticity, while also having the capacity to take advantage of new input. Therefore, an intriguing path would be to determine how adult neurogenesis, with its neuronal turnover and cortical development-like environment, would affect structural plasticity. In essence, adult neurogenesis is akin to deprivation studies where competition with loss or gain of new input (neurons) drives structural rearrangement, as we will next outline.

Adult neurogenesis as an extreme form of adaptation

The first studies to probe structural plasticity in neurogenic regions focused on the olfactory bulb because of its superficial and dorsal location making it accessible for imaging with a 2-photon microscope. Two-photon imaging was performed on adult-born immature periglomerular and granule cell neurons over multiples days to track their structural changes with their incorporation into the circuit [20•]. During early stages of development, the neurons extended their structure, but the dendritic elaboration eventually plateaued once the cell matured with its complete dendritic structure and spines established. This study, and further work, revealed that even months after the cells' complete growth, the granule cell spines and their glutamatergic postsynaptic sites remained dynamic with an estimated 20% daily turnover [20•,21•]. Further work showed that even cells that were 14-months old still retained these high dynamics, and therefore likely throughout the life of the cell [22•]. Additionally, granule cell spines relocated in an activity-related manner, most likely guided by fine 'spine head filopodia' [23].

Owing to its deep brain location, the hippocampus was initially out of reach of *in vivo* 2-photon imaging of adult-born neuron development. A recent study using a titanium implant to tunnel through the cortex and CA1 allowed longitudinal *in vivo* imaging of adult-born cells to track their dendritic development [24]. When mice experienced an enriched environment, the early dendritic outgrowth was accelerated, but upon maturation, neurons reached the same dendritic length. In another study, enriched environment was also shown to promote an expansion in the populations of presynaptic neurons contacting new granule cells, particularly in afferents from the entorhinal cortex [25•] and similar effects, including enhanced short-term plasticity, were observed with running [26]. Such levels of structural and functional remodeling may recruit entirely new circuits and alter preexisting connections.

Electron microscopy reconstructions showed that adult-born neurons form connections with entorhinal inputs primarily on multi-synapse boutons, and the authors suggested this may be a mechanism for hijacking the preexisting connections [27•]. A similar type of competition was observed for the establishment of functional synapses by terminals of new granule cells on pyramidal neurons of the CA3 region [28•], between adult-born and preexisting GC spines [29] and in synaptic strength plasticity [30]. However, in a study where, pre-existing dentate granule cells were genetically silenced for up to 6 months, their mossy fibers were largely maintained, suggesting an overall stability of preexisting axons despite

the competition from newborn granule cells [31]. Nonetheless, structural plasticity induced by neurogenesis in the hippocampus might differ from that in olfactory bulb because evidence points to an overall net addition, rather than replacement of granule cells in the dentate gyrus [32]. If this is the case, competition might play a lessened role. However, further assessment is required on the survival of dentate granule cells generated from both adult neurogenesis and development.

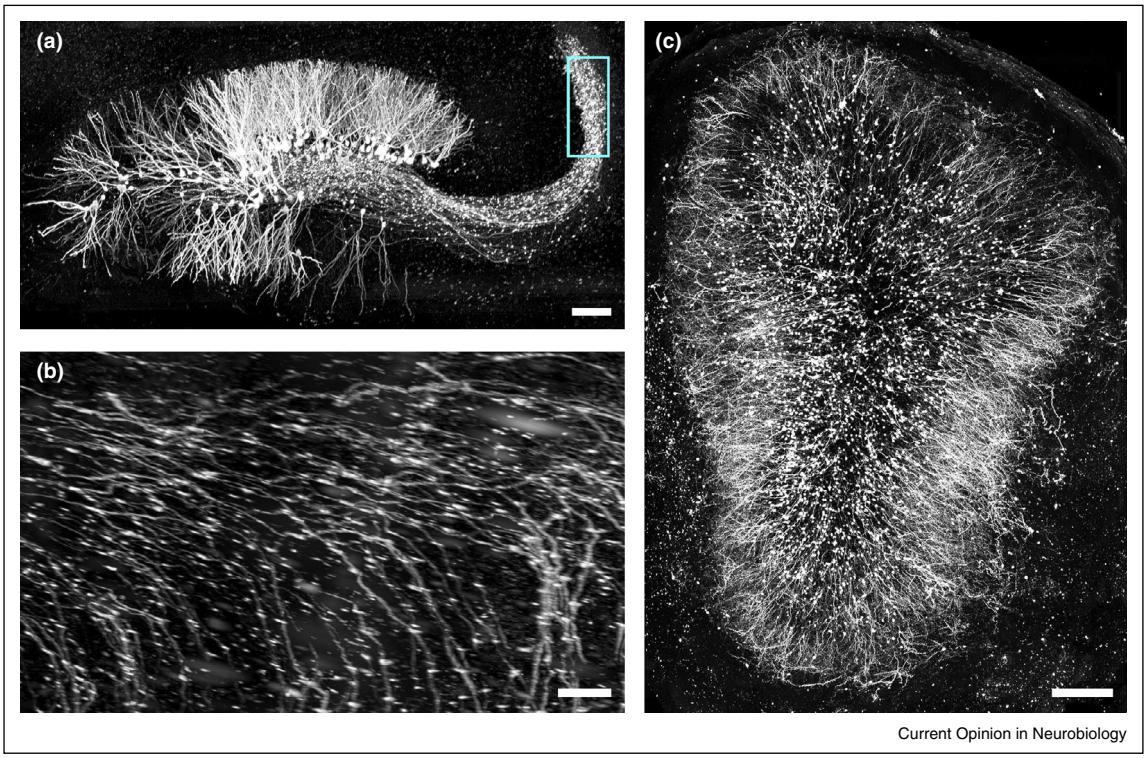
Quantification of the impact of adult neurogenesis on connected circuits

Although numerous studies have quantified the time course of adult neurogenesis using DNA-analog techniques for measuring relative changes in proliferation and survival rates, the absolute, total daily neuronal production in mice is still unclear. Bromodeoxyuridine (BrdU) is the most common used analog with a 150 mg/kg dose being sufficient to label all actively dividing progenitors with an estimated bioavailability from 15 min to 2 hours, depending on the study [33,34]. The magnitude of adult neurogenesis may be greatly underestimated in studies that use this single-dose regime of BrdU or with retroviral labeling of adult-born cells, since only dividing progenitors undergoing s-phase during this period, along with their progeny, are labeled.

Using serial end-block imaging, complete reconstructions of the olfactory bulb and hippocampus were made after a single injection of oncoretrovirus [35•]. Even with this brief labeling interval, it was possible to appreciate both the significant number of neurons produced when projected in a large volume of sampled tissue (1-mm thick), and more so, the density of adult-born neuron neuropil in these brain structures (Figure 1).

To determine the impact of adult-born neurons on the pre-existing, directly connected, primary neuronal circuits, we must first accurately assess the total number of neurons. In the rat hippocampus, it has been approximated that 9000 new cells are created per day [34] and when scaling this to young adult mice, this value is reduced by 70% to 2700 per day [36]. Additionally, only about 30% of these cells survive to be neurons beyond 4 weeks, a time point when they have developed their complete dendritic and axonal structure. Therefore, approximately 800 neurons per day (although this may be a low estimate), or 24 000 per month, are created that

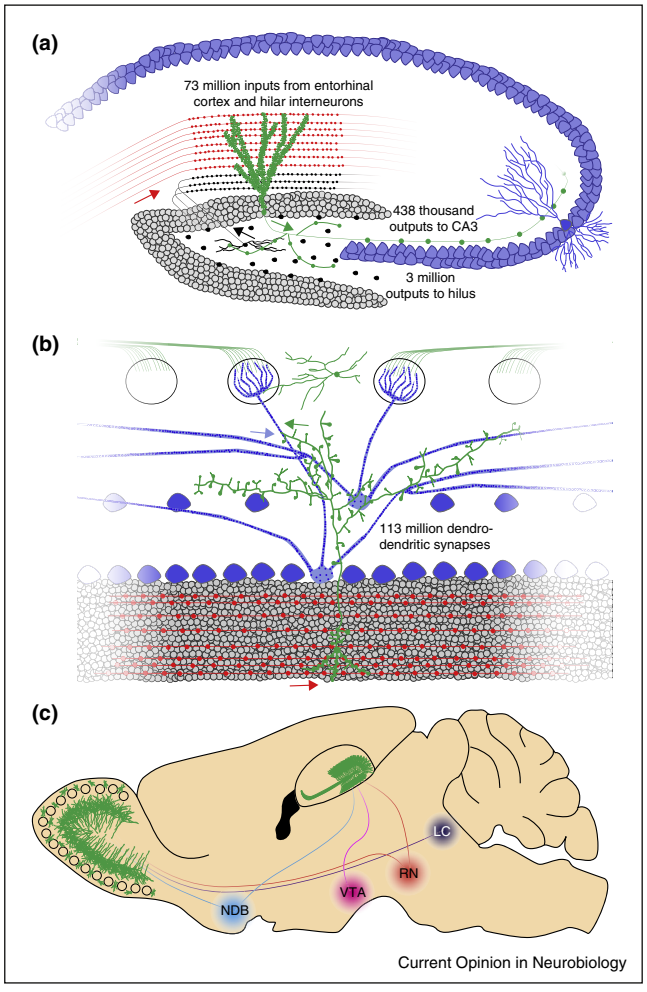
Figure 1



Adult neurogenesis causes great changes in local circuitry. **(a)** 1 mm thick coronal projection image of dentate gyrus 2 months after a single retroviral injection expressing green fluorescent protein with adult-born granule cells labeled and their axonal projections to CA3. **(b)** Horizontal projection of axonal projections (from (a) blue box) into CA3 with puncta being putative synapses. **(c)** 1 mm thick coronal projection image of olfactory bulb 3 months after a single retroviral injection expressing green fluorescent protein with adult-born granule and periglomerular neurons labeled. Scale bars = (a) 100 μm, (b) 80 μm and (c) 200 μm.

survive beyond 4 weeks. Multiplying this by the number of granule cell dendritic spines (input) and axonal boutons (output) in the CA3 [27•,35•], with adult-born granule cell input, about 70 million presynaptic entorhinal and hilar interneuron synapses and with adult-born granule cell output, about 3 million hilar interneuron and 400 thousand CA3 synapses would need to be added or changed each month (Figure 2a). It has also been calculated in rat that the number of adult-born granule cells generated in a month is as large as ~60% of the total population cortex stellate cells of the entorhinal cortex and ~30% of the CA3 pyramidal neurons [34].

Figure 2



Local and long range connectivity monthly changes due to adult neurogenesis. **(a)** Cartoon of adult hippocampus showing an adult-born granule cell (green) receiving input from entorhinal cortex (red fibers and arrow) and hilar interneurons (black cells, fibers and arrow) with output to CA3 (blue pyramidal cell) and hilar interneurons (green fibers and arrow) with daily synaptic changes to accommodate new neurons. **(b)** Cartoon of adult olfactory bulb showing adult-born granule cell (green) making dendro-dendritic synapse (green and blue arrows) with mitral and tufted cells (blue neurons) while also receiving significant top-down input from the piriform cortex (red fibers and arrow). In the glomerular layer (open circles), two neuron populations also undergo adult neurogenesis: periglomerular neurons (green neuron) and olfactory sensory neurons (green fibers) that also cause significant daily synaptic changes. **(c)** Cartoon showing long-range modulatory inputs to the two neurogenic zones. NDB: nucleus of the diagonal band of broca, VTA: ventral tegmental area, RN: raphae nuclei and LC: locus coeruleus.

Using similar calculations in the olfactory bulb for granule cells, 30 000 new neuroblasts arrive into the OB per day [37] where 40% survive beyond 4 weeks to integrate into the circuit, making a daily total of 12 000, or 360 000 adult-born neurons per month [38•]. Taking the average dendritic length and spine density and multiplying this by the total number of neurons [22•,39•], about 100 million dendro-dendritic synapses per month would be required to change for accommodating the new neurons (Figure 2b). Moreover, olfactory bulb granule cells receive tremendous top-down input from the olfactory cortex (mostly from the anterior olfactory nucleus and the anterior piriform cortex), although the total numbers of synapses on a given granule cell are still unknown, it can also be assumed that significant synaptic re-arrangement needs to occur in these inputs. Even though these numbers are small compared to the billions of synapses in the complete brain structure, the impact of this turnover on pre-existing, intrinsic and extrinsic, bulbar circuits must be highly relevant at the functional level.

In addition to glutamatergic inputs to the adult-born cells, in the olfactory bulb, granule cells receive local GABAergic input, strong top-down glutamatergic input from the olfactory cortex, noradrenergic input from the locus coeruleus, serotonergic input from the dorsal and medial raphe nuclei and cholinergic input from the horizontal limb of the diagonal band (Figure 2c) [40]. In the hippocampus adult-born cells receive GABAergic inputs from local circuitry, cholinergic input from the diagonal band of Broca, serotonergic inputs from the raphe nuclei, and dopaminergic inputs from the ventral tegmental area (Figure 2c) [41–43]. Interestingly, the first synaptic inputs that adult-born granule cells of the olfactory bulb receive are from cholinergic fibers [39•]. These approximate numbers illustrate the widespread remodeling that occurs in neurogenic networks and indicate that preexisting host circuits must have substantial plasticity as required to accommodate new incoming presynaptic and postsynaptic partners [44]. Further 'connectomic' studies to quantify all connectivity will be of great advantage to truly know the impact of adult-born cells on host circuits.

Adult neurogenesis promotes structural plasticity in host circuits

What evidence exists of structural plasticity induced by adult neurogenesis? The first study to explore this concentrated on olfactory bulb mitral and tufted cell principal neurons (collectively named M/T cells) that relay sensory information to the olfactory cortex. M/T cells directly synapse three major neuronal populations that undergo intense postnatal neurogenesis: olfactory

sensory, periglomerular and granule neurons (Figure 2b). *In vivo* imaging was performed to determine whether M/T cells have similar dynamics in their glomerular dendritic structure and it was concluded that M/T glomerular structure was remarkably stable, despite their direct connection to adult neurogenesis [45].

With the evidence of prolonged structural plasticity in adult-born granule cells of the olfactory bulb, we questioned whether the pre-existing, early postnatal derived granule cell population had similar dynamics or was instead stable, akin to what was observed in M/T cell structure. Using *in vivo* imaging, we found a high level of structural plasticity in the pre-existing granule cells that was identical to age-matched populations of adult-born neurons [22•]. Additionally, when tracking the dynamics of $GABA_A$ receptor clusters on M/T cells, the postsynaptic structure directly apposed with granule cell spines, we observed matching structural plasticity. These results demonstrate that adult neurogenesis is capable of driving structural, and therefore synaptic plasticity in its connected circuit of adult neurogenesis-derived and pre-existing populations of neurons, implying the constant influx of new neurons requires continual remodeling of the existing circuit.

Consistent with this notion, excitatory inputs onto developing granule cells, both in the olfactory bulb and in the hippocampus, display enhanced levels of functional plasticity [46,47•]. The expression of this potentiated plasticity might depend not only on the properties of new cells, but may also require atypical forms of plasticity expressed in their presynaptic partners. The contribution of host circuits to the remarkable capacity for activity-dependent plasticity, awaits to be investigated.

How far can adult neurogenesis drive brain plasticity?

We have outlined directly connected circuits associated with adult neurogenesis and propose further study to examine how the neurogenic regions coordinate pre-existing neuron function with the integration of new neurons. Additionally, with such dramatic plasticity demanded by the addition and loss of complete neurons, it would be interesting to see whether this turnover drives plasticity in more far-removed circuits, both upstream and downstream. Although there is no direct study examining downstream plasticity, a recent study utilized 2-photon imaging of the structural plasticity of CA1 pyramidal neuron spines and found them to be highly dynamic [48]. This plasticity in CA1 occurs two synapses downstream from the dentate gyrus and it would be relevant to determine whether altering adult neurogenesis can affect these spine dynamics and also in further removed networks. Along these lines, adult neurogenesis in the olfactory bulb might mirror the ongoing neurogenesis of olfactory sensory neurons located in the olfactory epithelium [22•].

Future perspectives

Understanding the mechanisms of the host circuitry in accepting and guiding the integration of adult-born cells is important for deciphering the steps of adult neurogenesis and also for potential stem cell-based therapies. Interestingly, in the olfactory bulb, adult-born cells must first 'listen before being able to speak' within the circuit, with inputs onto adult-born cells developing before output synapses [49]. This may be a mechanism to foster the newborn cells while protecting the network from improper connectivity. This appears to be unique to adult-born cells and may be a specialized feature of pre-existing neurons within the local circuit. Another important feature is the requirement for competition in the circuitry to drive plasticity, which is a common theme in both adult neurogenesis [50••] and in sensory deprivation studies in the cortex [18]. Having a void in connectivity by inducing a focal brain injury, was also shown to be necessary for successful embryonic stem cell transplantation into the brain [51•].

What special features exist in the neurogenic regions that allow such plasticity in the pre-existing population? A neurogenic region must certainly provide signals to drive neuronal differentiation of immature cells, but also local cues to allow new neurons to integrate properly. The extent to which these signals are related is unclear. For instance, in the adult cerebral cortex, local injury allows neurogenesis to be forced from non-neurogenic glial progenitors, but new neurons generated under these conditions remain largely immature [52]. This arrested development might be due to the limited potential of glial-derived neurons or to the limited capacity of the host network to allow appropriate integration of new functional units. Dissecting the mechanisms that control the potential for plasticity and the limitations imposed by different regions of the adult brain, will become essential.

In conclusion, adult brain non-neurogenic regions, despite their lack of a supportive 'niche' to guide the integration of new neurons [53], specific manipulations have unmasked a hidden capacity for structural plasticity. Likewise, circuits associated with adult neurogenesis may also undergo structural remodeling to accommodate circuit input/output changes induced by new neuron integration. Therefore, it is interesting to determine the influence of neurogenesis on non-neurogenic connected circuits in local and distant regions of the adult brain, which could provide valuable insights into the potential of adult neurogenesis for driving plasticity beyond the niche.

Conflict of interest statement

Nothing declared.

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