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Adult human neurogenesis: A view from two schools of thought

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ABSTRACT

Are we truly losing neurons as we grow older? If yes, why, and how can the lost neurons be replaced or compensated for? Is so-called adult neurogenesis (ANG) still a controversial process, particularly in the human cerebral cortex? How do adult-born neurons -if proven to exist- contribute to brain functions? Is adult neurogenesis a disease-relevant process, meaning that neural progenitor cells are dormant in adulthood, but they may be reactivated, for example, following stroke? Is the earnest hope to cure neurological diseases justifying the readiness to accept ANG claim uncritically? These are all fundamental issues that have not yet been firmly explained. Although it is completely understandable that some researchers believe that we can add new neurons to our inevitably deteriorating brain, the brain regeneration process still possesses intellectually and experimentally diverting views, as until now, there has been significant confusion about the concept of ANG. This paper is not intended to be an extensively analytical review distilling all findings and conclusions presented in the ANG literature. Instead, it is an attempt to discuss the commonly entertained opinions and then present our reflective insight concerning the current status quo of the field, which might help redirect research questions, avoid marketing an exaggerated hope, and more importantly, save the ever-limited resources, namely, intellectuals' time, facilities, and grants.

Evolution of the concept

Adult neurogenesis (ANG) refers to 'the birth of neurons in the adult brain where progenitor cells with proliferative potential are the foundation of neurogenesis' (Ming and Song, 2011). Thymidine-H3 labeling technology (HA Johnson, 1961) and the thymidine analog bromodeoxyuridine (BrdU) were introduced to identify the birthdate of cells, where this marker is supposedly incorporated into DNA during S-phase of the cell cycle and thus is widely considered a marker of DNA synthesis (Kaplan and Hinds, 1977). Although many researchers have identified BrdU in the granule cells of the dentate gyrus and olfactory bulb postnatally, it was later reported that these labeled cells declined rapidly with increasing age (Goldman and Nottebohm, 1983; Snyder et al., 2009). Additionally, BrdU incorporation can produce errors in cell fate specification and even cause morphological and behavioral abnormalities, most likely due to inconsistency in BrdU dosing and frequency of administration (Kolb et al., 1999). For instance, BrdU-labeled cells observed in the white matter subjacent to the cortex did not colabel with the neuronal marker TuJ1and were distributed along blood vessels or myelinated fibre tracts; thus, they were probably newly generated endothelial cells or oligodendrocytes (Lewis, 1968; Rakic, 2002). Such methodological limitations make BrdU labeling one of 'the most misused techniques in neuroscience' (Taupin, 2007; Rowell and Ragsdale, 2012). Moreover, most distinguished ANG reports have investigated very young rodents and knowing that rodents can live up to approximately 3 years (Hughes & Hekimi, 2016), it is highly possible that most results reported in ANG literature could represent neurogenesis only during childhood, which seems consistent with the results seen in children, where no more neurons are added after approximately 18 months of age (Ackerman S, 1992).

Later, many studies in different species were published. Among them, a study suggested that new neurons are continually added in adulthood in the macaque monkey neocortex (Gould et al., 2001). Around the same time, the first study on humans was published nearly three decades after the birth of the ANG hypothesis in rodents (Altman, 1963). Eriksson et al. reignited the field by siding with Altman and suggested that new neurons are generated in the dentate gyrus of adult humans (Eriksson et al., 1998). However, Eriksson et al. employed a

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very small sample size and insufficient control data. Moreover, all samples were not collected from healthy individuals given that brain metastasis in untreated cancer patients is not unlikely, particularly in cases of head and neck squamous cell carcinoma (Ruzevick et al., 2013). Furthermore, Eriksson et al. clearly reported that they found an 'apparent decline in the number of cells that are detected in the patients that had the longest interval between BrdU treatment and histological assessment'(Eriksson et al., 1998; Mathews et al., 2017).

Unexpectedly, postnatal birth of human hippocampal neurons was later reported by studying the correspondence between the ^{14}C concentration in neuronal genomic DNA and the atmospheric ^{14}C concentration after the date of birth of the subjects (Spalding et al., 2013). In this study, genomic DNA of hippocampal neurons of individuals born before nuclear bomb testing during the Cold War was found to have higher ^{14}C concentration than the atmosphere compared to individuals who were born after bomb testing. Although the results based on the ^{14}C dating method are considered valid evidence of ANG by some researchers (Roeder et al., 2022), it was reported that ^{14}C dating method is not a foolproof method to assess neurogenesis, as it is vulnerable to how one processes the sample and has yet to be validated in animal models (Gandhi et al., 2019; Sorrells et al., 2021). Furthermore, since ^{14}C concentrations in genomic DNA corresponded to the time around the birth of the individual, most neurons must be as old as the person (Bhardwaj et al., 2006). Moreover, it is not yet clear whether the levels of adult neurogenesis correlate with cognitive abilities in humans (Kuhn et al., 2018). This is supported by the fact that the overall rates of cellular proliferation are dramatically reduced in the adult brain relative to the developing brain, and these rates continue to decline throughout old age (Hattiangady et al., 2008; Bonfanti and Charvet, 2021).

Discussion of the arguments

The realization that neurons in adulthood are not renewed was introduced initially in 1887 by Giulio Bizzozero (G. Bizzozero, G. Vassale, 1887) and later confirmed by Ramón y Cajal who observed a paucity of mitotic divisions and a lack of transient forms from simple to more complex neuronal morphologies (S Ramon y Cajal, 1928). However, the introduction of 3 H-thymidine (3 H-dT) autoradiography and BrdU labeling for detecting cell proliferation revealed that, unlike most somatic cells that are continuously renewed or can be regenerated, neurons behave as a nonrenewable epithelium (CP Leblond, 1964). A recent paper reported that some radial glia-like (RGL) cells in the adult human hippocampus exhibit high levels of proliferation (Terreros-Roncal et al., 2021). However, the authors failed to show an example of radial glial cells colabeled with proliferation markers (Alvarez-Buylla et al., 2022; Arellano et al., 2022). Although BrdU-labeled cells were identified throughout the cerebral wall, including the neocortex, these were identified as nonneuronal cells and thus do not substantiate the claim of neurogenesis in the normal adult primate neocortex (Kornack and Rakic, 2001). Furthermore, evidence shows that the stability of the nuclear structure in neurons provides an explanation not only for why cortical neurons cannot divide, but also for why they usually die if they replicate their DNA (Aranda-Anzaldo and Dent, 2017). Nevertheless, to overcome the proliferation dilemma, the notion of quiescence of neural stem cells has been introduced. Some researchers believe that adult neural stem cells are maintained in a state of reversible cell cycle arrest under normal conditions (Lugert et al., 2010; Urbán, 2022), whereas pathological conditions, such as seizures stimulate and deplete them (Fu et al., 2019). However, the quiescence notion does not seem to be supported by evidence. For instance, homeodomain-Only Protein (HOP) has recently been described as a quiescent NSC marker in the adult dentate gyrus (Berg et al., 2019), whereas other report found that HOP-expressing cells in the hippocampus were not proliferating either in healthy control tissue or after experimental seizure induction (Alshebib et al., 2021). Thus, HOP protein could be an additional crack in the glass ceiling of the ANG notion.

Doublecortin (DCX) is currently considered a transient molecule expressed during neural development and is commonly used as a marker for immature neurons. The presence of adult neurogenesis in the adult human hippocampus is still documented mainly by immunolabeling with doublecortin (Terreros-Roncal et al., 2021), although DCX is not selectively expressed in newborn neurons (Sorrells et al., 2021). For instance, DCX was also expressed in astrocyte (Verwer et al., 2007), and DCX was also found not required for 'survival and maturation of adult-generated hippocampal neurons' (Dhaliwal et al., 2016; Merz and Lie, 2013). However, another hypothesis has introduced to justify the nonproliferating status of DCX-expressing cells, which is neurogenesis without division. For instance, a study showed that DCX-positive cells in the cortex and non-neurogenic parenchymal structures seem to be generated during embryonic development (Piumatti et al., 2018). Since then, some research groups have named these cells non-newly generated immature neurons (nng-IM) and they believe that these cell populations represent a brain reserve (Gómez-Climent et al., 2008; La Rosa, et al., 2019). However, it has been reported that dormant neuronal precursors maturation and integration observed using DCX promotor in the adult piriform cortex of transgenic mice seem to be used sparingly throughout the lifespan (Klempin et al., 2011), besides that the number of dormant precursors is inherently limited by their non-proliferative nature and thus, the immature, non-newly generated neurons could not be an explanation for the significant discrepancies in interpretation of recently published results of Boldrini et al. (2018) and that of Sorrells (Sorrells et al., 2019). Furthermore, it has been shown that the origin and fate of the so-called dormant neuronal precursors are fundamentally different (Feliciano et al., 2015), and the analysis of maturation and connectivity is so far limited to species in which a transgenic reporter system is available (Ribic et al., 2010; Rotheneichner et al., 2018). Despite well-preserved morphological and molecular features as suggested by La Rosa team (La Rosa et al., 2020), the distribution of cortical immature neurons was highly heterogeneous, particularly in neocortex, which could explain that the dormant neuronal precursors are a novel type of neuron and new coding element in the adult brain rather than simple addition or replacement for preexisting network components (Benedetti et al., 2020). Moreover, some researchers believe that antigen retrieval methods may induce nonspecific immunoreactivity (Sorrells et al., 2021). Additionally, most studies on adult neurogenesis have used the NeuN antibody as a neuron-specific marker. However, the NeuN protein can be expressed by several nonneuronal cells, and thus, the specificity of NeuN for neurons seems to be limited (Rakic, 2002a, 2002b; Yu et al., 2020). Moreover, some neurons fail to be recognized by NeuN at all ages (Sarnat et al., 1998). For instance, major neuronal cell types appear devoid of NeuN immunoreactivity including cerebellar Purkinje cells, olfactory bulb mitral cells, retinal photoreceptor cells, Cajal-Retzius cells, inferior olivary and dentate nucleus neurons, and sympathetic ganglion cells (Mullen et al., 1992; Sarnat et al., 1998).

Although some researchers seem to be convinced that neurogenesis exists in the adult hippocampus and olfactory bulb, they deny the existence of ANG in the neocortex (Rakic, 2002a, 2002b; Kornack and Rakic, 2001; Bhardwaj et al., 2006; Huttner et al., 2014). The existence of ANG in the hippocampus and not in the cerebral cortex seems to be a baseless comparison, as it is already known that both the cerebral cortex and hippocampus are involved in higher cognitive functions; thus, a concept that applies to the hippocampus should also be unequivocally applied to the cerebral cortex. Additionally, our principal concern is understanding how ANG, if proven to exist in the cerebral cortex and hippocampus, is implicated in brain diseases and how we could translate the ANG hypothesis into its clinical potential to manage and cure human brain injuries and diseases. Rakic et al. seem in disagreement with the hypothesis of ANG in the cerebral cortex, and even more so regarding ANG in the human cortex, where they clearly stated that none of the billions of the cortical neurons are generated locally (Rakic et al., 2007). Moreover, cortical cells must migrate to their final destinations, and therefore, the human cerebral cortex is not generated in adulthood but

perinatally (Bhardwaj et al., 2006). This hypothesis is consistent with the conclusions of a previous publication that used regression theory to model the timing of neural development in the brains of different species suggesting that humans are neurally advanced at birth relative to the other species studied (Clancy et al., 2001), given that endogenous regenerative capacity has limits in mammals relative to other species (Martino, et al., 2011; Cayre et al., 2021) and that the mechanisms underlying the regenerative failure of neurons are still largely undetermined (Varadarajan et al., 2022). This statement seems in agreement with a recent study that found that once organoid culture reached approximately 9 months, its gene expression shifted to resemble that of cells from human brains soon after birth (Marton and Pașca, 2020). Although the cells of the intestinal epithelium are replaced every 2 weeks and those of skin are renewed every few months, it has generally been accepted that neurons in most structures of the mammalian brain are generated during restricted developmental periods (CP Leblond, 1964).

The back-and-forth disputation around ANG seems to be highly resistant to a resolution, where Boldrini et al. recently reported that hippocampal neurogenesis in healthy humans persists throughout life (Boldrini et al., 2018), while other researchers have almost simultaneously reported a completely opposite conclusion showing that neurogenesis in the human hippocampus drops sharply in children to nearly undetectable levels in adulthood (Sorrells et al., 2018; Cipriani et al., 2018; Arellano et al., 2018), and similarly in the human olfactory bulb (Sanai et al., 2011). However, this is not to be confused with the synaptic rewiring and synaptic pruning processes that are not complete until later in life, approximately at 25 years of age (Arain et al., 2013) or even older depending upon the environment and genetic makeup. Taken together, there seems to be no true conflict between all major neurogenesis reports starting with Cajal, then Altman and Rakic, and ending with Sorrells and Boldrini, who all seemingly agree on the existence of ANG in the hippocampus, at least in rodents, while disagreement is still strong concerning ANG in the cerebral cortex of rodents and even more pronounced regarding neurogenesis in the human cortex. This could be because the ANG notion was initially introduced as an enthusiastic extrapolation, which was nearly universally rejected at the time when Altman had first identified replicating 'glial cells' in rats and cats—not in humans—and based on that, he speculated that such a finding supports the possibility that new neurons may be formed in forebrain structures (Altman, 1963). Interestingly, dividing satellite glia have also been described in the adult neocortex of several mammals (Mareš & Brückner, 1978; Korr et al., 1983).

Afterward, matters assumed a continuous snowball effect where a small ball of zealous speculation made by Altman started rolling and continued gathering many supporting reports that are currently resistant to opposing explanations. However, researchers who are in favor of ANG-dependent plasticity, at least in the hippocampus, clearly stated that 'an overarching unifying theory that embeds neurogenesis-dependent functionality and effects on connectomics is still missing' (Kempermann, 2022), a confession that is confirmed by mounting evidence using different modern technologies. Although modern technologies are supposed to demystify accumulative misunderstanding through their precise findings, the ANG conflict seems to persist. For instance, a recent report has shown the possibility of ANG in the human hippocampus using a single-nucleus RNA sequencing approach (Zhou et al., 2022), while another report using the same technology and published nearly simultaneously suggests that hippocampal ANG is likely lost in humans (Franjic et al., 2022). The eloquent rule says that 'extraordinary claims require extraordinary evidence'. However, 'doubts around ANG remain in each link of the logic chain, and crucial supportive quantification of adult-born neurons is missing' (Nowakowski and Hayes, 2001).

Despite the ongoing ANG controversy, there appears to be a kind of reconciliation between the opposing paradigms with clear unanimity of opinions that the current discrepancy exists only concerning ANG in human, and not in other species, particularly in rodents. However, it seems that two schools of thought have already been established concerning the ANG hypothesis: Altman's school, which is in favor of the concept (pro- ANG), and Rakic's school, which is obviously against the ANG hypothesis (anti- ANG), at least in the human cerebral cortex, arguing that humans only get the neurons they are born with. It seems that the dominant reason why some scholars still believe that no adult-born neurons are added to the cerebral cortex is that 'the stability of the human neuronal population may be a biological necessity for the retention of long-term memory and learned behavior over the lifespan, since we rely heavily on acquired knowledge soaked up through schooling and experience' (Rakic, 1985; Rakic, 2002a, 2002b; Abraham and Robins, 2005) and that the 'brain is considered to be a nonrenewable organ composed of fully differentiated neurons' (Jacobson, 1991). Interestingly, adult mammals with large complex brains such as dolphins and whales that encounter complex memory and navigational challenges, do not appear to have new neurons in their hippocampi (Patzke et al., 2015; Parolisi et al., 2018), which makes it plausible that species longevity or increased brain size constrains neurogenesis (Paredes et al., 2016; Charvet and Finlay, 2018; Snyder, 2019). Furthermore, evidence shows that the postmitotic state of cortical neurons depends on the high stability of its underlying nuclear structure, which becomes an insurmountable energy barrier for karyokinesis and mitosis (Aranda-Anzaldo and Dent, 2017). This also seems consistent with the neurotrophic hypothesis of neural survival and neuroplasticity introduced by Levi-Montalcini (Levi-Montalcini and Hamburger, 1951). Certain neurotrophic factors, such as the nerve growth factor family have been shown to support the survival of particular types of neurons (Lindsay, 1995). For instance, a study showed that the administration of NGF prevents the atrophy and death of axotomized cholinergic neurons in the adult central nervous system (Barde, 1990). Similarly, another study showed that neurotrophins directly introduced into central nervous system lesions rescue degenerating neurons (Aubert et al., 1995). In a similar manner, the neurotrophin hypothesis for synaptic plasticity suggests that neurotrophins participate in activity-induced modification of synaptic transmission (Schinder and Poo, 2000; Castrén and Antila, 2017; Colucci-D'amato et al., 2020). Although it has been reported that the control of neuronal survival depends on the provision of trophic molecules, it has also been observed that activity, humoral factors, and trophic support from glia contribute to neuronal viability (Barres and Raff, 1993). Consistently, mature neurons become extremely resistant to triggers that mimic neurodevelopmental cell death such as neurotrophic factor withdrawal (Rita Levi-Montalcini & Booker, 1960; Chen et al., 1977; Easton et al., 1997; Putcha et al., 2001).

Aging leads to impairment of numerous physiological systems, including both the innate and adaptive immune systems (Oh et al., 2019; Brauning et al., 2022). Immunosenescence is a new concept that reflects age-associated restructuring changes in innate and adaptive immune functions (Eduardo Fuentes et al., 2017). As a result, elderly individuals do not respond to immune challenge as robustly as young individuals (Montecino-Rodriguez et al., 2013; Müller, 2021). In fact, dementia seems to be immune-related disease closely associated with aging and thus, focusing on enhancing the immune system seems to be an anti-aging measure. Although the brain could be the primary control biopanel orchestrating almost all biological processes in our bodies, aging is not just losing neurons and thus, continuous addition of new neurons to maintain a healthy brain during adulthood does not always entail an overall healthy body and healthy life. Furthermore, the brain consumes approximately 20% of glucose-derived energy, and most of the energy is used for synaptic activity (Harris et al., 2012; Mergenthaler et al., 2013). Interestingly, it has been reported that cerebral blood flow is higher in children and adolescents and drops with aging (Melamed et al., 1980). Additionally, new findings show that two analogs of the lymphatic system do exist in the central nervous system, namely, the glymphatic and meningeal lymphatic clearance systems (Tian et al., 2022), adding to the documented role of osteocalcin in brain signaling which is a

multipurpose osteokine secreted by osteoblasts (Shan et al., 2019). However, all these biological process seem to exhibit a functional decline with aging (Sun et al., 2018; Mäkinen, 2019). Thus, investing more time in understanding how to enhance cerebral blood flow, and cerebral lymphatic clearances in addition to cultivating the promise of the neurotrophic hypothesis to reasonably maintain healthy preexisting neurons seems to be a worthwhile endeavor.

Conclusion

To summarize, a growing body of evidence indicates that neurogenesis seems to be a childhood-restricted process, at least in humans. This seems consistent with children's developing theory of mind, where cognitive skills are typically sculptured during early childhood (Mayes and Cohen, 1996; Meltzoff and Gopnik, 2013). Thus, paying more attention to the other mechanisms that potentially control neurogenesis processes in children is a pragmatic step, given that most brain pathologies, including psychiatric disorders can evidently be traced back to very early in life (Fryers and Brugha, 2013; Liu et al., 2015; Lippard and Nemeroff, 2020). The negative clinical consequences could be caused by physical and psychological abuse, low levels of environmental richness, and even false moral indoctrination (Woolley and Wellman, 1990; Baillargeon et al., 2010; Thompson, 2012; Wilson et al., 2020). Therefore, regarding the tantalizing hypothesis of ANG, we reiterate what Nobel prize awardee Prof. Yamanaka courageously stated concerning the many challenges that need to be addressed to successfully translate the technology of pluripotent stem cells (PSCs) to clinical practice, including their inherent property of tumorigenicity, where he wrote: 'this question should be answered only by science, not by politics or business' (Yamanaka, 2012). Although the physical basis of several higher cognitive functions, such as memory, still seem undecipherable, the brain has many other secrets to be explored regardless of our current capabilities. As of now, neurons seem to be a key element in the nervous system that represents the uniqueness of every individual.

CRediT authorship contribution statement

The authors confirm contribution to the paper as follows: manuscript conception and design: Alshebib Yasir. Draft manuscript preparation: Alshebib Yasir, Tomokatsu Hori, Atul Goel, Asra Al Fauzi, and Taichi Kashiwagi. All authors reviewed and approved the final version of the manuscript.

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Disclosures

The authors have no competing interests to declare.

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