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Neurogenesis In Adults: From Biology To Behaviour

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ABSTRACT: The concept of Neurogenesis in adults in the brain region specified as Hippocampus is the most remarkable process due to the uniqueness and budding impact on the cognition level of an individual but also to its localized vertical integration of different scales of neurosciences ranging from molecular and cellular biology to behavior. This occurs primarily in the subventricular zone of the lateral ventricles and the sub granular zone of the dentate gyrus in the hippocampus. Thus, it is a process which is build up pf various steps through which neurons are produced from adult dividing neural stem cells and migrate to be amalgamated into existing neuronal circuits. In this review article, the researcher seeks to help illuminate the concept of adult neurogenesis by providing an overview of the basic concept starting from its inception to its timely evolution. The current paper also focuses on the pros and cons of adult neurogenesis in humans along with all the challenges that one may face in the research with the possible potential solutions. Thus, the author in the paper focuses on and suggests neurogenesis as a potential target for therapeutic intervention for a number of disorders and that make neurogenesis a unique case study for how different parameters in neuroscience can link together.

KEYWORDS: Adult neurogenesis, neural stem cells, hippocampus, cognition, subventricular zone, lateral ventricles, neuronal circuits.

INTRODUCTION

The area of neurogenesis has made considerable development during the last two decades. Less than 20 years ago, the neuroscience community had a limited understanding of adult neurogenesis. Despite being documented using a variety of approaches, the concept that immature neurons continue to be absorbed into the adult brain was not widely acknowledged until the mid-1990s.Neuroscientists debate the possibility of neurogenesis in mature humans. While some researchers report that neurogenesis declines dramatically as the human brain ages, other show that neurogenesis in the dentate gyrus (DG) of the hippocampus of human brains continues into old age. A better understanding of the evidence supporting the concept of adult human neurogenesis is critical because its presence or absence can affect the foundations upon which our understanding of learning and memory mechanisms is built, particularly in relation to aging and the pathogenesis and management of many neuropsychiatric disorders. If neurogenesis does not occur in the adult hippocampus, other conceptions of neuroplasticity, such as alterations in synaptic transmission or remodelling of existing neurons, may rise to the forefront of thought regarding brain activity and dysfunction.6 In this review, we will introduce the basic notion of neurogenesis and provide a historical background. We also examine the present status of research on neurogenesis in adult humans and assess how the concept of neurogenesis has influenced current treatment of neuropsychiatric illnesses.

Neurogenesis is the creation of new neurons, which is characteristic of a developing brain. Neurogenesis in an adult animal brain is stated to occur in the lateral subventricular zone (SVZ) and the DG of the hippocampus. Rats, mice, song birds, and nonhuman primates have all demonstrated direct evidence of adult neurogenesis. There is indirect but significant evidence of neurogenesis in adult people. In many animals, particularly those with robust olfactory function, such as rodents, considerable adult neurogenesis in the SVZ has been seen. In mammals, newly generated neurons move to forebrain areas, specifically the olfactory bulb, and integrate into the olfactory neural circuitry. Subventricular neurogenesis is rudimentary in humans and is thought to contribute to olfactory neural circuitry and olfaction, though evidence is not explicit. Neurogenesis in the adult human DG has been postulated to play a role in memory and learning systems, as well as in protecting the brain from stress-induced attrition.

DEPICTION OF NEUROGENESIS

It is critical to briefly explain the methods for tracing new neurons, as the approaches employed to mark a dividing and maturing cell frequently alter the nature and interpretation of the research discussed below. The most frequent way for marking dividing cells is to incorporate a traceable molecule into DNA. Because DNA synthesis is often limited to mitosis, at least at detectable quantities, it has been employed as a marker of neurogenesis. The initial neurogenesis experiments used tritiated (3H) thymidine (10), which allowed for radiographic tracing of cells that were born at the time of injection. Another thymidine analogy, BrdU, was created in the 1990s because it could be identified using immunohistochemistry. This breakthrough was critical since immunolabeling allowed for the fate identification of dividing cells by combining it with additional markers such as the neuronal marker NeuN or the glial marker glial fibrillary acidic protein (GFAP). BrdU labelling, along with its sister molecules IdU and CldU (for their iodide and chloride counterparts,

respectively), is still commonly utilized, owing to its ability to measure both proliferation rates and survival. BrdU, while beneficial, is not a perfect marker for a variety of reasons, including possible toxicity, no specificity (damaged cells may incorporate it), and histological restrictions.

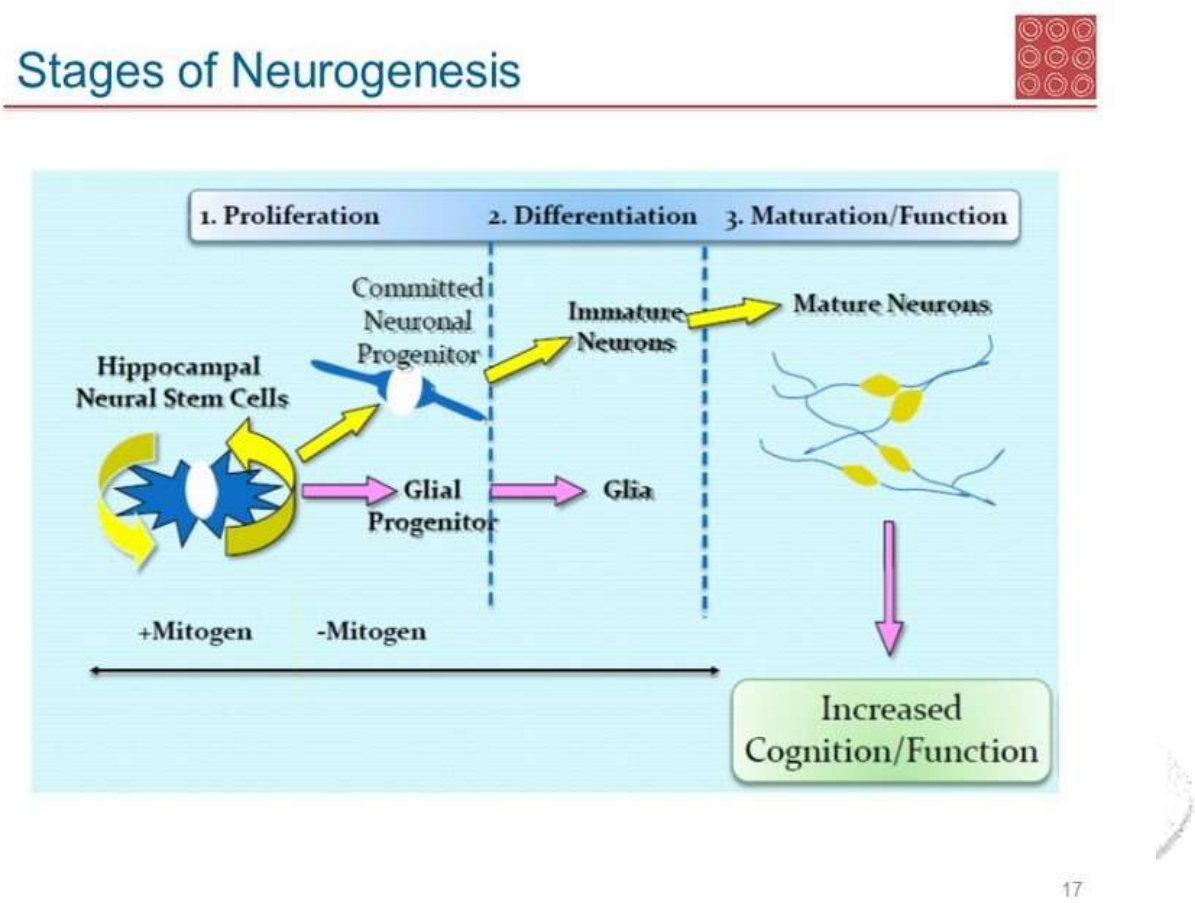

Figure 1: Stages of Neurogenesis in Adult Brain

HISTORICAL PRESPECTIVE

Since the birth of the "neuron doctrine" in 1894, a vital precept of contemporary neuroscience theorizing that the nervous system is made up of distinct individual cells, the general consensus for many years was that neurons could not regenerate in the adult brain.

The first evidence of adult brain neurogenesis came from Joseph Altman in the 1960s from his studies in rats. However, Altman's experimental evidence in rat was not robust enough. At that time, adult neurogenesis in either the animal or human brain was not known at all, and any such concept was considered improbable, so his evidence was ignored by the scientific community. In the 1980s, Fernando Nottebohm of Rockefeller University published the first clear evidence of adult neurogenesis in song birds. Over time, more studies were conducted in animal models, particularly rodents, and the results were supportive of continued neurogenesis. One study reported that *de novo* neurons in the hippocampus of adult rats showed similar membrane properties and were functionally equivalent to mature granule cells and, hence, could integrate into existing circuitry to influence hippocampal functions.

Kornack and Rakic, using BrdU (a thymidine analogue that labels DNA) and cell-specific markers, reported evidence supporting continued neurogenesis in the hippocampal region in adult macaque monkeys, though they estimated the rate of neurogenesis was 10 times less than in rodents. Another study reported finding BrdU labelled cells in associative neocortical regions in adult macaque monkeys, which the investigators suggested provided evidence for newly formed neurons; however, the study was criticized for not considering alternative explanations. A later study reported conflicting results after examining cell-specific markers that showed that newly formed cells in the new cortical regions in macaque monkeys were not neurons, though the authors supported that the presence of newly born neurons in the olfactory bulb and hippocampus was possible. On the other hand, a study in dolphins, porpoises, and whales—known for their large brains, longevity, and complex behaviour similar to humans—reported that these mammals had relatively small hippocampi that lacked neurogenesis.

The concept of adult neurogenesis in humans was first proposed in 1998 when Eriksson et al reported affirmative evidence of neurogenesis in the hippocampus after examining the postmortem tissue from patients with cancer who were injected with BrdU for therapeutic purposes. Knoth et al reported evidence of neurogenesis in the individuals 0 to 100 years of age after identifying protein markers for various stages of neurogenesis. Investigators used postmortem brain tissue samples and neurogenesis markers were identified using immunohistochemistry. In 2011, Sanai et al reported the discovery of the rostral migratory stream in the human brain, suggesting a rudimental continued olfactory neurogenesis. This was shown in postmortem tissue from the human brain. Rostral migratory stream (RMS) is said to carry precursor neuronal cells from the SVZ to olfactory neuroepithelium. RMS is, by default, active in the brains of animals and humans of foetal age, and as well as in many adult animals, but its presence in the adult human brain has been controversial. Another study reported observing neurogenesis in postmortem samples of human striatum, including migration of newly formed interneurons to the neocortex measuring the concentration of the nuclear bomb test derived radioactive carbon (C14) in genomic DNA, though no additional studies have been conducted that lend support to these results. C14 present in the environment gets integrated into the genomic DNA of the dividing cells in the body. In individuals born after 1955, around the time of the nuclear bomb tests, individuals started to show a higher concentration of C14 in their genomic DNA reflecting the higher environmental levels post-tests. At any time, newly formed cells of the body will reflect the environmental concentration of C14, which can be accurately estimated. This fact has been exploited by the investigators of this study for the retrospective birth dating of the neuronal cells in the human brain to prove adult neurogenesis. The brain tissue samples for this study were collected from the postmortem human individuals admitted for the autopsy and tissue banks.

FUNCTIONAL ASPECTS

Research across many laboratories has painted an increasingly complete picture of how new neurons contribute to hippocampal function (Abrous and Wojtowicz, 2015; Christian et al., 2014). These studies support the view that adult neurogenesis is not needed for learning per se but rather for an advanced level of functionality. The new neurons allow the spatiotemporal contextualization of information and they help avoid catastrophic interference in the hippocampal network, promoting ‘behavioural pattern separation.’ They

facilitate the integration of new information into pre-existing contexts and help to clear the dentate gyrus at the circuit level and, at least in this sense, support forgetting. In addition, as the hippocampus is part of the limbic system, new neurons are involved in affective behaviours. The new neurons contribute synaptic plasticity to the dentate gyrus, measured as increased long-term potentiation (LTP; (Ge et al., 2007; Marín-Burgin et al., 2012; Schmidt-Hieber et al., 2004). All other neurons are massively inhibited by the local interneurons. At a given time, synaptic plasticity in the dentate gyrus is thus concentrated in a defined, functionally naive sub-set of (new) neurons. This unique mechanism of focusing plasticity sets this neuronal network apart from all others studied to date. In this context, the number of new cells required for a functional benefit is actually very low. As an important and influential discussion point, Pasko Rakic has famously argued that adult hippocampal neurogenesis would not be possible in humans because the adult human brain has to Favor stability over plasticity in order to accomplish its computational tasks (Rakic, 1985). Current theories usually argue the other way around: it is exactly its amazing plasticity that has made the human brain so flexible and successful. The question is: what is the contribution of new neurons to this success? As adult neurogenesis is spatially limited, this contribution cannot be general, as most brain regions, including the neocortex, work without it, but its effects might still be strategic. Simple brains are highly effective but in their "hard-weirdness," they are hardly adaptable. Adult hippocampal neurogenesis is a prime tool for adaptability and seems to be a solution to the specific computational challenge in the dentate gyrus. Without it, yet another solution to the plasticity-stability dilemma as seen in rodents would need to have evolved in humans. Whether such a parallel solution is likely or not remains to be discussed but the functional contribution that new neurons would make to human cognition is not negligible.

EVOLUTIONARY CONSIDERATIONS

The mammalian dentate gyrus as we see it in rodents and primates, including humans, is an "add-on" structure that evolved late phylogenetically and developed late ontogenetically. Signs of adult hippocampal neurogenesis have been detected across essentially all land-born mammalian species, that is except for the aquatic and possibly some flying mammals (Kempermann, 2012). Dolphins, however, despite their ascribed 'intelligence,' have a habitat that is profoundly different from humans, and they have an exceptionally small hippocampus and a cortical architecture that differs massively from terrestrial mammals. By all standards, humans are more like mice in this respect.

Adult hippocampal neurogenesis evolved with the dentate gyrus; it shows little resemblance to the more diffuse neurogenesis found in the non-mammalian equivalents. Additional comparative studies are still needed, but the hypothesis is that adult hippocampal neurogenesis is an advanced solution to a particular network situation that delivers added specialized functionality to the hippocampus – including in humans. Sorrells et al. argue that there is no condensed sub granular zone stem cell niche or neurogenesis in humans and thus that such continuity in function might not exist, but this cannot be concluded from the presence or absence of marker proteins alone. The described functional relevance of adult neurogenesis is dependent on the availability of 'immature' neurons with reduced inhibition and high synaptic plasticity, not on precursor cell proliferation or intermediate progenitor cells per se.

Neocortical development is an example of where, in the human brain, a common developmental principle has evolved to greater complexity: a precursor cell population that is only transient in mice and rats became the foundation of the massive expansion and gyrification of the neocortex in primates (Fietz et al., 2010). However, the basal progenitor cell that allowed this step at least transiently also exists in mice. With respect to adult neurogenesis, a key difference between rodents and humans might therefore lie in the specific qualitative and quantitative relationship between precursor cell proliferation, a hypothesized non-proliferative waiting state, a period of high synaptic plasticity, and the lasting integration of the new neurons.

The contribution of such highly plastic 'neurons in waiting' not only depends on the number of cells but also on the duration of this critical time window of enhanced plasticity (Kempermann, 2012). The period of DCX expression appears to be about a month long in humans as it is in mice, but species might still differ in that respect. In any case, full maturation of newborn neurons might take several months in primates (Kohler et al., 2011), resulting in a heterogeneity of the granule cell population with a relatively large subpopulation of early 'neurons in waiting' with delayed final maturation.

Different mammalian species might have developed different solutions to the problem of how to provide a critical population of highly plastic cells to the network. For example, the red fox (Vulpes vulpes) has very high numbers of DCX-positive cells but very low levels of proliferation, which is quite different from mice (Amrein and Slomianka, 2010). The balance between retained neurogenic potential from proliferating progenitor cells or from a reservoir of pre-generated, highly excitable cells might also vary between human individuals (see discussion above and (Spalding et al., 2013). In addition, this balance is likely to change across the life span. If the duration of the window of plasticity lengthens with age, extremely low numbers of proliferating cells could still contribute to a reservoir of plastic cells that sustain the required functionality. To some extent, this functionality also seems to be additive, in that past neurogenic events also lastingly change the networks (because the new neurons survive for long durations with presumably 'normal' levels of synaptic plasticity), so that aged individuals might actually require lower numbers of new neurons.

The process of adult neurogenesis may somewhat parallel what occurs in the female reproductive system of mammals, where all stem cell proliferation that generates the population of egg cells occurs very early in life and further development is delayed. The case of adult neurogenesis might not be as extreme, depending on if the study by Sorrells et al. or Boldrini et al. best reflects the situation, but there is no fundamental need for substantial stem cell proliferation in adult neurogenesis to extend throughout the ever-expanding life span of humans. There might also be a 'neurogenic menopause,' in which the potential is used up, and this might indeed contribute to age-related cognitive decline.

RESEARCH CHALLENGES AND POSSIBLE SOLUTIONS

Due to the rare availability of optimum human brain tissue and limitations of study methods that can be used in living humans, designing a robust study on neurogenesis that can exclude the many confounding factors seen in previous studies is a challenge. Possibly integrating the methods and approaches of both the Sorrells and Boldrini studies to a single design might yield results with an additional level of coherence, though it

might also give rise to additional questions. A robust proposition would be to conduct a series of collaborative experiments by these two groups with specific, targeted objectives. Also, the use of bioinformatics methods to analyse the differential expression of neurogenesis signature markers, as per maturation stages in developmental transcriptome (prenatal to adult ages) in human hippocampus, might contribute additional clarity. This has been partly tried by Sorrells et al when they compared the developmental transcriptome of human hippocampus with that of macaque monkeys and found them comparable in expression of marker proteins.

A lack of non-invasive and safe investigatory methods has hampered neurogenesis-related research in living humans to a considerable extent. Relatively safe neuroimaging approaches, which can detect growth of newly formed cells in and around neurogenic niches and their integration in the existing neural circuitry with high specificity, might be a solution. The use of novel techniques in stem cell biology—such as induced pluripotent cells, which is to generate neural stem cells from a patient's own cells; and developing brain organoids from the derived neural stem cells, which facilitate study of the three-dimensional growth of the cells—might be an additional non-invasive approach to study disease-specific effects on adult neurogenesis in humans.

CONCLUSION

Regarding adult hippocampal neurogenesis in humans, many questions remain unanswered. Species differences are interesting and important, and the report by Sorrells et al. reminds us that simple 1:1 translation from animal studies to humans are problematic. But the coincident publication by Boldrini et al., which is more in line with the current body of knowledge briefly summarized in the present article, not only further questions the categorical claim that there is no adult neurogenesis in the human hippocampus but also points out the direction in which this kind of research will develop: towards a more quantitative analysis that aims at relating neurogenesis parameters to other features of plasticity and to behaviour in health and disease. There is a clear need for additional ways to study the generation of new neurons in adult humans. A more complete analysis of cell phenotypes and potential differentiation trajectories, by for example single cell RNA sequencing, is likely to provide valuable information. Methods for following the process of adult neurogenesis in vivo would be extremely valuable, particularly for assessing changes under different conditions and in pathology. Since the serendipitous discovery of adult neurogenesis by Joseph Altman (Altman and Das, 1965) and the heated discussion about 'Limits of neurogenesis in primates' (Rakic, 1985) after Fernando Nottebohm's description of adult neurogenesis in songbirds in the 1980s, the field has come a long way and amassed a more than critical and multifaceted body of evidence supporting the existence of adult neurogenesis in human brains. Human evolution might have found very efficient ways to balance proliferation and the duration of the critical maturation period in order to provide the level of hippocampal plasticity that the individual requires.

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