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Recalibrating the Existence of New Neurons in Adult Brain

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ABSTRACT: New neurons were shown to born throughout adulthood, a process known as neurogenesis. Last year, the human hippocampal neurogenesis field was flipped on its head by a paper in *Nature* from Sorrells et al. questioning the presence of human hippocampal neurogenesis during adulthood (Sorrells, S.F. et al. 2018 *Nature*, *555*, 377−381). Now, a new study by Moreno-Jiménez et al. reported that human brain can make new neurons well beyond middle age until the tenth decade of their life, and earlier studies have failed to find the neurogenesis due to its flawed methods. This paper also finds that production of new neurons drastically drops in patients suffering from Alzheimer's disease. Here, we discuss key findings of this paper, emphasizing how improved protocols and tissue preservation lead to visualization of adult neurogenesis and further highlighting in what way this drop of neurogenesis in Alzheimer's disease brain could possibly open new roads to therapy.

KEYWORDS: *Adult neurogenesis, hippocampus, Alzheimer's disease, neuron, human, dentate gyrus*

Adult neurogenesis in the brain, once thought to be absent in mammals, is now known as a continuous and robust process present in the subventricular zone (SVZ) of the lateral ventricles and subgranular zone (SGZ) in the dentate gyrus (DG) of hippocampus. There is a growing body of evidence for adult hippocampal neurogenesis (AHN) in humans, but whether that neurogenesis is sufficient enough to contribute to brain function has been debated. The revolutionary report by Eriksson et al. demonstrated that SGZ of hippocampus is one region where adult neurogenesis takes place in adult humans and this process is continued throughout life.[1] In several animal models, a decrease in adult hippocampal neurogenesis has been implicated in the pathophysiology of brain disorders involving neuron loss, such as stroke, cerebral palsy, and Alzheimer's disease. These results have further postulated the question of whether abnormalities in adult DG of the hippocampus have been implicated in the pathophysiology of neuropsychiatric diseases in humans. It is anticipated that if adult neurogenesis can be used in a controlled manner to replace damaged neurons, then it may be possible to repair and regenerate neurons lost to injury, disease, and aging. Therefore, new neurons during AHN may be exploited to develop new treatments for neurologic diseases based on neuroregeneration and repair. However, studying AHN in humans is highly challenging due to methodological challenges, and human hippocampal neurogenesis alteration in disease conditions is poorly understood.

Last year, a seminal report by Sorrells et al. aroused great disbelief among neuroscientists by finding the absence of AHN in humans.[2] Approximately at the same time, another paper from Boldrini et al. reported that AHN persists throughout aging.[3] These two papers have been recently summarized discussing their key findings and potential reasons for conflicting results.[4] Now, this intense debate about whether adult hippocampal neurogenesis happens in humas seems to be settling down after a recent paper by Moreno-Jiménez et al. in *Nature Medicine*.[5] This elegant study has reported that new neurons are born throughout adulthood until late stages of aging in healthy people but sharply drops in people suffering from Alzheimer's disease (AD).

Generation of new neurons pass through various phases from neural stem-cell-like progenitors, intermediate progenitors, neuroblasts, immature granular neurons, and mature granular neurons. All these distinct stages are identified by the presence of specific protein markers through immunohistological markers (see Figure 1). Doublecortin (DCX) is commonly used as a proxy marker for neuroblasts, and it is expected that some of these DCX+ neuroblasts will ultimately develop into mature neurons. Various studies have shown the existence of DCX+ neuroblasts throughout a lifespan ranging from neonatal to adolescence until old age. Contrary to this view, last year, Sorrells et al. reported that neurogenesis drops sharply after early development and is absent by adulthood, and thus stimulated the rebirth of the old dogma about the existence of AHN in humans.

It is important to note that tissue preservation is very vital for detection of DCX+ neuroblasts. In fact, a longer fixation time may mask the various antigens including DCX, which therefore may look absent despite being present. Indeed, some of the samples in Sorrells et al. have come from brain banks where brain tissues are usually fixed in paraformaldehyde (PFA) for many months, thus making it hard for the antibody to bind to antigen. Examining adult human brain is also hard due to autofluorescence, resulting in less sensitivity. Moreno-Jiminez et al. looked at the tissue fixation issue and reported that DCX+ neuroblasts drop sharply after 48 h in PFA while they were undetectable after 6 months. Additionally, they chose a well-preserved brain sample with a shorter postmortem

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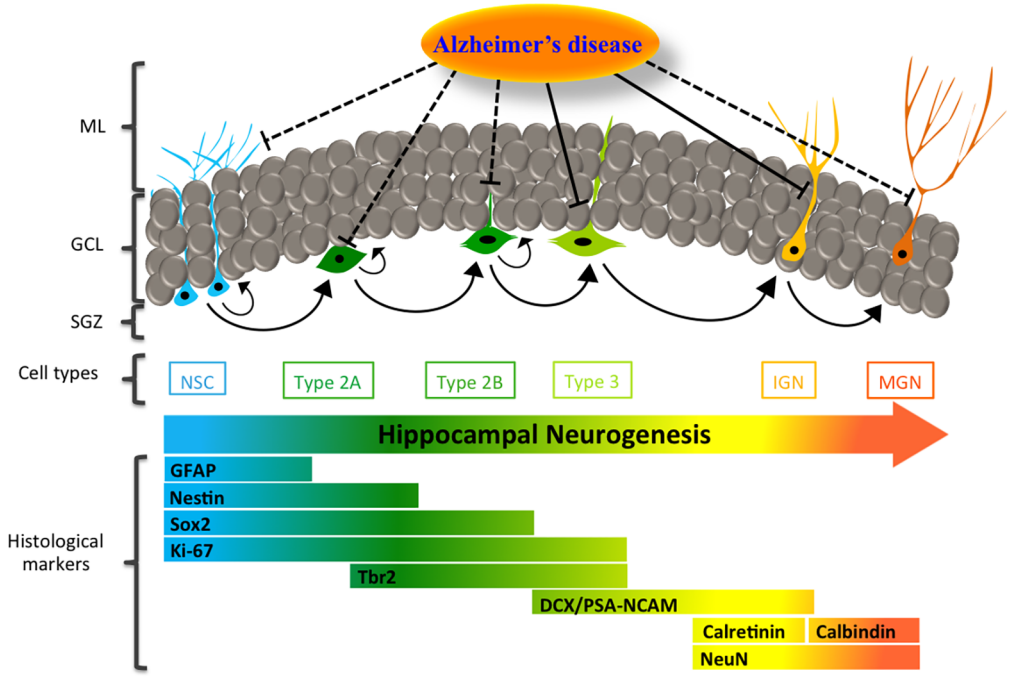

Figure 1. During adult hippocampal neurogenesis in humans, the number of immature neurons drops drastically in AD. Neural stem cells (NSCs) divide to generate type intermediate progenitors (IPs) 2A, type 2B in SGZ. These IPs are further differentiated into type 3 to immature granular neuronn (IGN) and mature granule neurons (MGN). This lineage progression is accompanied by changing TF expression that is distinguished by various histological markers. Type 3 and IGN are reduced in AD but whether NSC, type 2A, 2B, and MGN are affected in AD remains to be determine (shown with dashed line).

interval (PMI) as opposed to a previous paper that used large variable PMI.

Moreno-Jiménez et al. have preserved brain tissue from 13 deceased healthy adults, ranging from 43 to 87 years of age. They used DCX+ neuroblasts in combination with other markers such as Prox1, Calretinin, NeuN, and Calbindin, which are related to various neuronal maturation stages. These neurons had smooth and undeveloped branches, which fit the criteria for newly generated young neurons. They have found approximately 42000 immature neurons/mm^2 in the youngest donor that died at the age of 43. The number for these neurons drops by roughly 30% during late aging, which is consistent with previous observations and doctrine that AHN declines with age. In fact, Moreno-Jiménez et al. found that the density of DCX+ immature neurons were as high as proliferative neuronal population densities during peak neurogenesis, due to increased sensitivity and adjusted protocol. This suggests that earlier studies may have actually underestimated AHN and it is a more robust phenomenon than ever thought. To claim that what they are seeing is indeed neuroblasts, they have also used other neuroblast markers such as PSA-NCAM, in addition to DCX. However, it is important to note that it is hard to know the duration for which neuroblasts remain in that phase and when they transit to mature neurons.

Then Moreno-Jiménez et al. evaluated the brain tissue from 45 patients aged 52−97 years that were suffering from AD. The hippocampus is the main region of the brain that is affected in AD. Researchers looked at immature neurons in those patients and found that people suffering from AD had 30% less neurons than those of healthy individual of the same age. Importantly, they also found that neurogenesis drops very sharply and progressively as AD advances. These results demonstrate the presence of immature neurons in AHN throughout physiological and pathological aging in humans until the tenth decade of life. Although these results need to be reconfirmed by other researchers, this raises a thought provoking idea of whether slowing down this sharp decline might slow down AD. Most of the AD therapies are focused on modulating the pathway that can target amyloid-β and tau proteins, but we are far from reaching that goal. At this stage, we are not sure if halting this sharp neurogenesis decline will lead to therapy, but this report strongly suggests that treatment of AD should also focus toward targeting neurogenesis that in turn may provide novel therapeutic approaches.

Taken together, this recent study provides well-defined, conclusive confirmation that human hippocampal neurogenesis continues throughout life, but whether this conclusive study will put the ongoing debate to rest remains to be seen. At the moment, we may now be self-assured and move forward that what we usually see in mice and other animals will be pertinent in humans as well. However, it is important to note that this new study also raises further questions about putting more focus at neural stem cells that could make new neurons and further dissecting the process by which newly formed neurons integrate into existing circuitry in physiological as well as pathological conditions.

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Author Contributions

J.D. and M.T.A. contributed equally to the work. P.P.T. originated the concept of writing the manuscript. P.P.T. wrote the manuscript. M.T.A. made the figure. J.D., S.C., and S.G. helped in the discussion during writing of the manuscript.

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Notes

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