BORN THIS WAY OR CAN OUR BRAIN BE REWIRED?

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"Studying helps me to stay young." These are the words of Jan Warnink, who studied at the University of Leuven at the age of 80 years. He is not the only one taking this "it is never too late to start" spirit to a whole new level. In Italy, Giussepe Paterno received his bachelor diploma in history and philosophy at an impressive age of 97, and in Groningen, a lady of 88 years decided to study philosophy as well. Are they nuts for going to college as an elderly, or is there wisdom in doing a study after your retirement?

I was always told that if you want to achieve something, whether it was developing a skill or mindset, you should start at a young age. Once we grow old, we become more stubborn in our ways, and it is said that a large amount of effort is needed to get out of our comfort zone. However, this might not be so true after all. Although it was first believed that we are born with all the brain cells we will ever have, this idea has been proven wrong over the past years. It seems that our capacity to learn new things does not simply vanish once we grow old and that our brains are even able to grow new neurons over time. So, what does this mean? To what extent are we set in our ways when we are grey-haired? And, in the case of unlimited plasticity, are we able to influence the plasticity of our brain and become master learners?

The never-ending debate

Our brain is constantly reconnecting, creating new connections and strengthening existing ones. This so-called neuroplasticity improves communication inside the brain. At the core of neuroplasticity lies the process of growing new neurons and integrating them into neural circuits, referred to as neurogenesis. This process was always thought to only occur during the early life years [1]. However, more than a century ago, it was discovered that rats are capable of growing new neurons even during adulthood [2-4]. While this indicated that neurogenesis occurs in rodents, scientists had trouble figuring out the human situation. For over 50 years, studies on neurogenesis were bouncing back and forth on whether human adults neurogenesis existed or not. Until 2019, when Jason Snyder put a new, interesting idea forth [5]. He noted that labs investigating neurogenesis in mice used *young* mice, whereas human research was performed in *adults*. If we were to study humans and rodents relatively similar in age, we might find clarity about the existence of adult neurogenesis, or so he thought.

Although Snyder pointed out that the discrepancy in results between, as well as within, the rodent and human studies could be due to methodological differences, he was not convinced that adult neurogenesis in humans existed either. According to him, if adult neurogenesis does exist, then it exists at low rates and in very specific parts of the brain. Studies concentrating on the hippocampus found that rates of neurogenesis indeed varied throughout the lifespan in humans [6-8]. Human neurogenesis is found to be at its highest during the third month after we are born but persists throughout life at lower rates. However, why are neurogenesis rates lower at a later age? And, does adult neurogenesis serve a specific function?

Adult neurogenesis; function and significance

Nowadays, researchers are still not sure why and how newborn neurons are created. As the hippocampus is involved in learning and memory formation, some studies have highlighted the importance of newly generated neurons in learning, memory formation, and even in fear memories and spatial navigation [9]. One break-through article by Opendak and Gould dove into the literature and found evidence that silencing newly born neurons in adulthood results in memory impairment [10]. Opendak and Gould even suggested that newly generated neurons make connections with already existing ones [10]. It is thought that young neurons may help you adapt to a new environment or circumstances [10].

Adult life is full of changes; moving in and out of a new apartment, finding a new job, or changing your relationship status. It can be a struggle, and these challenges force us to be flexible and adapt to new circumstances. Of course, adapting to new circumstances requires us to learn from experiences and use this knowledge to our advantage. Newly generated neurons might help fine-tune the hippocampus, helping us adapt our responses to new environments [9]. For example, when shifting between jobs, you might be confronted with pesky co-workers, a condescending boss, or a demanding workload. Newly born neurons could play a key role in determining how you face those challenges.

Although the underlying mechanism remains unclear, the goal of adapting your responses to the new situations is more apparent, i.e. optimising survival strategies [10]. It is thought that newly born neurons help design a plan and prepare an individual on how to deal with stressful situations [11]. For an optimal survival plan it is important to know when to act and when to refrain. This skill requires one to distinguish between 'bad' and 'good' situations. This sounds easy, but it might be harder than you think. When we get older, it becomes harder to distinguish a person from a lookalike you met years ago. In order to do so, the hippocampus plays a crucial role in pattern separation: the process of distinguishing one memory from other, already stored memories [12, 13]. Deficits in pattern separation could lead to overgeneralisation of threats and the struggle to distinguish between safe and unsafe situations, which is often seen in patients with anxiety [14]. Mice with enhanced neurogenesis were better at performing pattern recognition tasks, and it has become clear that pattern separation depends on newly generated neurons resulting from neurogenesis [15-19]. The big question remains: can we influence adult neurogenesis and plasticity?

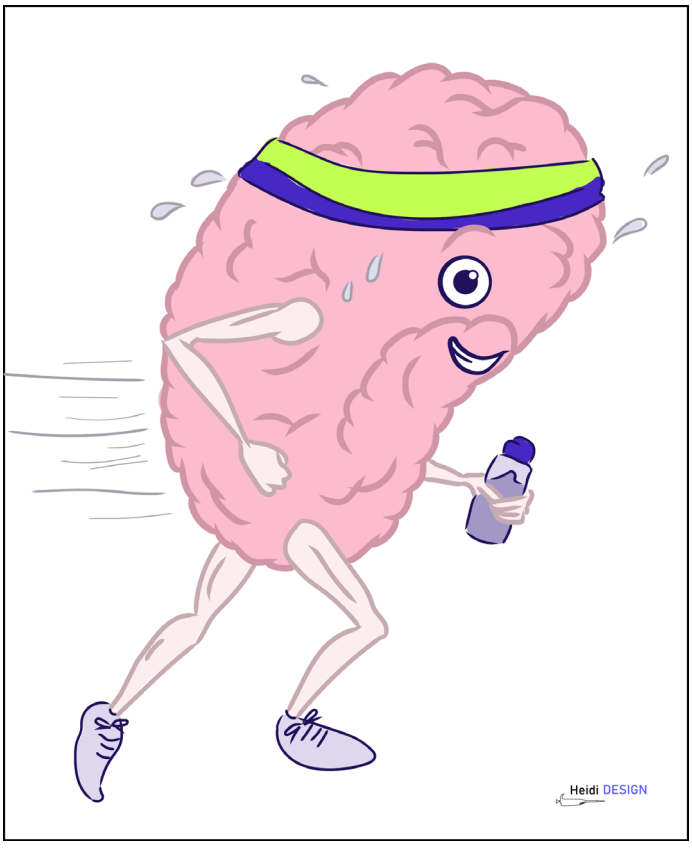
What influences hippocampal neurogenesis and plasticity?

In addition to Snyders observation that methodological differences might explain the discrepancy between and within human and mice research, two studies using methods similar to each other still found contradicting results. In 2005, post-mortem brains derived from different life stages (perinatal, postnatal, and adult samples) showed no newly born cells in hippocampal tissue [20]. However, these results are in contrast with a more recent study using a similar approach that observed both immature and newly adult-born neurons [6].

In other words, this last study found preserved neurogenesis. How could it be that these studies found contradicting results while using similar methods? It turns out there was a methodological difference all along. While the first study, reporting an absence of neurogenesis, obtained samples from individuals suffering from various diseases, the second study investigated samples of healthy individuals [6, 20]. What does this mean? Well, this means that diseases possibly disrupt neurogenesis and that a healthy lifestyle may be the key to prolonged neuroplasticity later in life.

Stress and antidepressants

Besides diseases, factors like ageing and stress do not benefit your brain condition either. The hippocampus is highly sensitive to stress, and this impact is even higher during periods of enhanced neuroplasticity, e.g. during infancy [21]. Hence, stress exposure in early life has been shown to have long-lasting effects on hippocampal neurogenesis and increases the susceptibility to developing disorders, such as depression, post-traumatic stress disorder, and Alzheimer's disease, later in life [22-25]. Additionally, patients with major depressive disorder show reductions in hippocampal volume, which may reflect reduced neurogenesis [26-28]. Moreover, hippocampal neurogenesis plays a key role in buffering stress responses in animals [29]. Hippocampal neurogenesis is currently investigated as a therapeutic target to improve the before-mentioned conditions, e.g. by antidepressants [30,31]. It is not exactly clear how, but antidepressants increase the expression of the *Brain-Derived Neurotrophic Factor* gene, which is needed for neurogenesis and plasticity [32-35]. However, this does not mean we should all run to the doctor to get a prescription for antidepressants. Lucky for us, there are other ways to increase your brain health.



Exercise

One way to promote neurogenesis and brain plasticity is by exercising. We already know that exercising is good for your physical health, but did you know it is good for your brain as well? A recent study in rats compared the effect of exercise on fear conditioning during adolescence and adulthood. Exercising rats had a higher expression of plasticity promoting genes, such as *Brain-Derived Neurotrophic Factor* [36]. Another study found similar results, reporting that rats that are exercising since adolescence showed an increase in amount, as well as complexity, of hippocampal doublecortin cells [37]. These immature neurons are used as a marker for neurogenesis. Moreover, exercise restores hippocampal plasticity and is associated with adaptive behaviour [32, 38, 39]. Exercise has both short- as well as long-term effects. For example, aged animals immediately improved their memory performance right after exercising, and sustained exercise boosted neurogenesis by promoting the connections between neurons and their integration into the communication network of the brain [32, 33, 40].

Environmental enrichment

Exercising is not the only way to improve your memory; putting yourself in a stimulating environment also influences the rate of neurogenesis [18]. This process is called environmental enrichment (EE), and it was first used by Donald Hebb, who raised rats in his home. He declared his pet rats were superior to laboratory-raised rats in terms of problem-solving abilities [41]. Nowadays, EE is not simulated by releasing rats in your home, but the animals are placed in big cages with small plastic toys, ladders, tunnels, running wheels, and sometimes a radio is placed near the cage. Scientists believe EE creates more opportunities to learn than a standard laboratory setting, and EE protects against age-related cognitive decline by stimulating neuroplasticity [42-46]. Moreover, a small period of only one week of EE is already enough to promote neurogenesis in mice [47]. Since the animals live in bigger cages, it is worth noting that an effect of exercising cannot be ruled out. Over the years, EE has remained largely a laboratory phenomenon, but it is currently investigated how these results translate to clinical settings. Maybe exposing yourself to a variety of experiences benefits your brain health as well.

Conclusion

After years of debate, the discussion on the existence of adult neurogenesis is finally settled. Human adult neurogenesis is real, and it is influenced by a number of factors, such as ageing, stress, exercising, and environmental enrichment. While ageing is inevitable, going for a walk, taking the time to relax, and challenging yourself to visit places you have never been before help to sustain the quality of your memory. Our brain is not a static organ and neither are we. So, whether you want to become a highly talented guitar player at a later age or want to make life-changing decisions, such as moving abroad or taking on a different career path: do not be afraid to do it! Your past experiences can help you handle difficult situations and help you thrive in whatever comes next, even if that is resuming a study after years of retirement. What is holding you back? Your brain certainly is not.

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