PERSPECTIVE

Exercise and hippocampal neurogenesis: a dogma re-examined and lessons learned

Exercise is a potent force of nature with significant potential for extending longevity and boosting physical fitness. It is also being increasingly used as a prophylactic and curative measure for various physical ailments, such as cardiovascular diseases and diabetes. Indeed, many of its benefits for the immune system, cardiovascular system, and even the microbiome are still being uncovered. However, perhaps where exercise may contain the most potential is in helping to unlock the mysteries behind neural regeneration, cortical plasticity, and cognitive enhancement. Although it has been known for a while that exercise yields numerous tangible benefits for mood, libido, spatial and verbal memory, and cognition—factors with strong underlying neural components—little has been known about why exercise has such a profound effect on the brain. As such, this paper will address the background and key findings regarding neurogenesis research, specifically concerning exercise-mediated neurogenesis, and detail overarching lessons that can be gleaned in order to establish general directions and guidelines for future research.

A monumental shift in the neuroscience field, in particular with regards to neural regeneration and plasticity, occurred after it was demonstrated for the first time that running stimulates neurogenesis in the dentate gyrus of mice (van Praag et al., 1999). This unexpected result came at a time when the dogma in the field posited that the number of neurons in the brain remains static after birth, with only the possibility of declining in number. However, it has been demonstrated that following proliferation, differentiation, and migration, these newly born neurons in the dentate gyrus that stem from exercise are then incorporated into the neural circuits of the hippocampus, the brain region critically important for memory consolidation and learning. Further research into this body of work has expanded our understanding of the factors that can lead to pronounced neurogenesis, such as enriched environments and aerobic exercise—with evidence suggesting that exercise and stimulating social and intellectual environments produce the same cognitive and neural effects in humans (Voss et al., 2013).

Once this now outdated dogma was flipped on its head, there was increased hope that this body of research could lead to new therapeutic creations for disorders of the nervous system. Exercise currently serves as a treatment option for major depression, and it also helps prevent the onset of and counteract Alzheimer's disease, dementia, and age-related cognitive decline (Laurin et al., 2001). A potential mediator between exercise and these health benefits is the phenomenon of neurogenesis, which raises the obvious question: What induces exercise-mediated neurogenesis? Although the precise answer is still not fully known, a recent publication reviews the role of a critical molecule in this process, brain-derived neurotrophic factor (BDNF) (Liu and Nusslock, 2018). As a member of the neurotrophin family, BDNF is vital for many of the functions central to neurogenesis, including proliferation, differentiation, maturation, and survival. Given that interest was initially sparked in BDNF for its role in neural plasticity, it is unsurprising to discover its importance for hippocampal neurogenesis.

Owing to greater experimental control in rodents, various genetic and biochemical assays have made dissecting BDNF's precise functioning in exercise-mediated hippocampal neurogenesis possible. For instance, although other environmental factors, such as a stimulating environment, have been shown to lead to hippocampal neurogenesis in rodents, BDNF may be unique in its role as a mediator between exercise and hippocampal neurogenesis in the rodent brain. It has been shown that metabolic derivatives from muscles and endurance factors stimulate BDNF expression in the brain and lead to improved spatial memory (Kobilo et al., 2011; Wrann et al., 2013; Moon et al., 2016). It should be important to note, however, that although BDNF plays a large role in neural plasticity and hippocampal neurogenesis, it is just one of many molecules in an ever expanding and comprehensive network of signaling pathways that guide neural proliferation and differentiation. Researchers have been able to uncover many signaling pathways and molecular cascades that converge on hippocampal neurogenesis. While this body of literature is vast and impossible to summarize here, it does provide insights into potential mechanisms for human neurogenesis.

With such experimental precision in rodent studies, the real question and scrutiny fall on hippocampal neurogenesis in humans, especially as it pertains to exercise. Does exercise-mediated hippocampal neurogenesis occur in humans? And if it does, could it be responsible for the anti-depressant, mood enhancing, and memory improvement effects of exercise? If it does not occur, then what is responsible for the cognitive and neural benefits of exercise in humans?

The precise molecular insights regarding BDNF and hippocampal neurogenesis from rodent studies have paved the way for better understanding this potential phenomenon in humans. Although it is harder to experimentally access the human brain, these rodent studies have translated nicely into useful proxies for understanding human neurogenesis. Indeed, there is increasing evidence that human hippocampal neurogenesis occurs, as assessed *via* more indirect measures. For instance, using 5-bromo-2-deoxyuridine (BrdU) tracing—which labels mitotically active cells—it was found that BrdU stained neurons in the dentate gyrus of terminally ill patients with presumably minimal exercise regimes (Erickson et al., 2011). Another study, using radiocarbon dating to track cell division in the brain, was able to find consistent neural turnover in the hippocampus (Spalding et al., 2013). Most convincingly, it has been shown that exercise, especially in moderation, increases the size of the hippocampus in humans, which is also linked to enhanced memory (Erickson et al., 2011). Moreover, cerebral blood volume as an *in vivo* indicator of hippocampal neurogenesis has been shown to correlate well with exercise in humans (Pereira et al., 2007) (**Figure 1**).

However, methodology for studying neurogenesis remains tricky in human studies, and the operationalized output is often ambiguous with regards to what is really being observed. This makes studying the role of BDNF in human hippocampal neurogenesis even more difficult.

Indeed, a recent study raises the possibility of reversing the dogma once again. Using immunohistochemical staining of various markers indicative of neural differentiation to localize subpopulations of neurons, the authors tracked hippocampal neurogenesis across various stages of life and found little to no

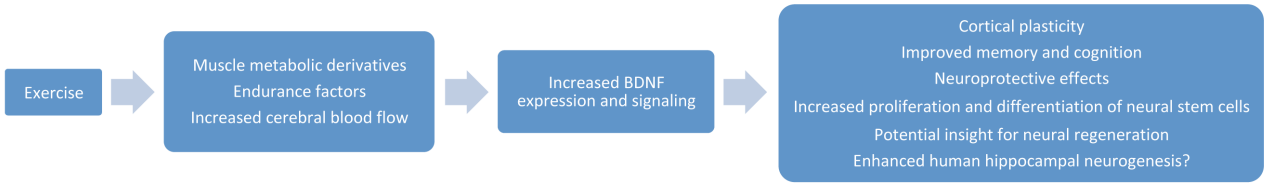

Figure 1 The connection between exercise and its cognitive and neural benefits involves complex signaling pathways, which include brain-derived neurotrophic factor (BDNF).

evidence of human hippocampal neurogenesis in adulthood (Sorrells et al., 2018). These findings are in direct contrast to decades of rodent and nonhuman primate research.

On one hand, these findings may simply testify to the difficulty of accurately studying human neurogenesis. It should be noted that this study did not study human hippocampal neurogenesis as a function of exercise, nor did it have the experimental power to manipulate other variables and record its effect on neurogenesis. However, its conclusion is still provocative and will spur continued exploration of human neurogenesis to either validate or debunk its findings.

Whether or not the results hold up to scrutiny, there are still significant takeaways from this rich body of literature and key areas of future research to be considered. For instance, with so much emphasis devoted to understanding the molecular mechanism of how hippocampal neurogenesis occurs, especially in mice, what is less studied but perhaps of more importance is why neurogenesis does not occur as robustly or at all in other brain regions. With the exception of the hippocampus and olfactory bulb—at least in mice—no other brain region is known to undergo adult neurogenesis. A thorough investigation into the factors that close this window of neurogenesis in other brain regions (for instance, work derived from research on critical period plasticity) may yield great benefits for neural regeneration therapies, especially when this body of work is combined with the molecular dissection of what stimulates hippocampal neurogenesis. Indeed, research on developmental critical periods and cortical plasticity will likely inform the neurogenesis field since neurogenesis is prominent in early developmental stages but much more silent in adulthood.

Regardless of whether human adult neurogenesis does occur or not, we should still exercise consistently. It is undeniably beneficial for mental and physical wellbeing. If there is one major takeaway from rodent research on this topic, perhaps it is that mice only exhibited hippocampal neurogenesis when allowed to voluntarily run, not when they were yoked to another exercising mouse. So find a physical activity that you enjoy, and wholeheartedly pursue it.

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