Why exercise is good for your brain

A closer look at the underlying mechanisms suggests that some sports, especially combined with mental activity, may be more effective than others

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On August 19, 1785, US President Thomas Jefferson shared the following advice with his 15-year-old nephew, Peter Carr: “Give about two [hours] every day to exercise; for health must not be sacrificed to learning. A strong body makes the mind strong” (http://avalon.law.yale.edu/18th_century/let31.asp). More than 200 years later, scientific research suggests that Jefferson’s aphorism is correct: various studies have demonstrated that physical activity reduces the risk of cognitive decline or dementia. For example, one study that analyzed nearly 20,000 men and women reported that midlife cardiorespiratory fitness correlates negatively with the development of dementia in advanced age [1]. Today, it is widely accepted that exercising keeps you mentally fit and is a useful preventive measure against Alzheimer disease.

But to effectively exercise against cognitive decline, more detailed instructions are needed. Is lifting weights in a fitness studio as good as jogging in the woods? Is dancing a good alternative? Can ‘brain jogging’ compensate for reduced physical effort? In recent years, animal studies have improved our understanding of the biological underpinnings that link physical activity to cognitive performance. This knowledge can now be used to inform the design of studies in humans.

There are several mechanisms by which physical fitness could modify mental performance. Exercising enhances the production of neurotrophic factors and increases cerebral blood flow; it improves cardiovascular fitness and may thereby protect the brain from risk factors for Alzheimer disease such as high blood pressure, heart disease, stroke, or diabetes. In addition, exercise specifically targets age-related cognitive decline and the

early phases of Alzheimer disease by promoting adult neurogenesis in the hippocampus.

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Most areas of the brain do not generate new neurons after birth, but the hippocampus maintains this ability throughout life: adult neurogenesis is required for specific types of learning and memory. Even so, as we age, neurogenesis in the hippocampus decreases and memory declines. Moreover, the hippocampus is one of the earliest brain regions affected in Alzheimer disease, and a deficit in learning and memory—particularly hippocampus-dependent learning—is one of the first symptoms. Physical activity may thus counteract memory loss in Alzheimer disease by supplying the hippocampus with new cells.

For a long time, neurogenesis in the mammalian brain was thought to stop after prenatal development. “In the adult brain, nervous pathways are fixed and immutable; everything may die, nothing may be regenerated,” proclaimed Nobel laureate Ramon y Cajal in 1913. This view prevailed for a long time, even after the first demonstrations of adult neurogenesis in mammals in the 1960s and 1970s. It took another 20 years until findings from several laboratories, most prominently those of Fred

Gage at the Salk Institute (La Jolla, CA, USA) and Elizabeth Gould, then at Princeton University (NJ, USA), gradually undermined the dogma. They demonstrated that neurogenesis continues into adulthood in two parts of the mammalian brain: the dentate gyrus of the hippocampus and, in most mammals, the olfactory bulb.

Shortly after this discovery, Gould showed that adult neurogenesis could be influenced by environmental factors and that stress has a negative impact. Gerd Kempermann, then a member of Gage’s laboratory—and now a professor at the Technische Universität Dresden, Germany, and at the German Center for Neurodegenerative Diseases—was intrigued by these results. “We thought that this negative regulation must be balanced by some kind of positive influence. Adult neurogenesis surely didn’t evolve just to be downregulated by stress,” he said. Together with his colleagues, Kempermann set out to look for such positive regulators in mice. “We gave them what we thought could be the opposite of stress. We tried to spoil them a little bit and give them a good life,” he explained. The team created what neuroscientists call an ‘enriched environment’—a larger cage with toys, tunnels, and running wheels—and found that adult neurogenesis was indeed increased in the hippocampus compared to littermates that were kept in standard laboratory cages [2].

An enriched environment, however, is a complex interplay of many components that go beyond a simple reduction in stress. It gives animals the opportunity for more social interaction and physical activity, and provides more possibilities for learning. Together with Henriette van Praag, then also in Gage’s laboratory and now a researcher at

the US National Institute on Aging (Baltimore, MD, USA), Kempermann analyzed the effect of the different aspects of an enriched environment separately. To investigate the contribution of exercise, the scientists simply added a running wheel to the cages of certain animals. They found that running increased the proliferation of neuronal precursor cells and, to a lesser degree, improved their survival [3].

Around the same time, neuroscientist Tracey Shors, Professor of Psychology at Rutgers University, USA, was also captivated by the phenomenon of adult neurogenesis and teamed up with Gould to investigate. 'Together we asked ourselves: Why are these new neurons in the hippocampus?' Shors said. As the hippocampus is involved in learning, Gould and Shors analyzed whether hippocampus-dependent learning affects the number of adult-generated cells. Indeed, it does: 'We were shocked that it worked so well,' Shors said. 'We found that the effect of learning is to keep cells alive. It is not making more cells, but it is making them survive.'

One important discovery Shors made is that the survival of the cells is dependent on whether or not the animals learn successfully. Animals that actually learned a skill

maintained more neurons than those that had the same amount of training but failed to master the task. 'I often tell my students that it is not enough to show up for the class, you do have to learn the material,' Shors explained. 'We want a biological mechanism that supports successful learning—not one that supports unsuccessful attempts.' Another relevant feature is effort. 'It's important that the task is sufficiently difficult and that the animal must devote considerable effort to learning,' Shors said. 'Tasks that are difficult to learn take longer. You are stimulating the hippocampal cells for a longer period of time.'

Exercise and learning tasks thus both impact on the hippocampus, but they do so by different means. Running mainly induces the proliferation of neuronal precursor cells, but many of the newly generated cells will die if they are not used. Learning is required to keep the cells alive. Researchers in Kempermann's laboratory have shown that combining physical and mental activity has an additive effect on net hippocampal cell number [4]. The full potential of exercising will only be realized if followed by an appropriate cognitive stimulus.

From an evolutionary point of view, this link between exercising and learning makes perfect sense. 'In animals, running and mental activity occur together,' Kempermann said. 'It is strictly human to sit motionless in front of a TV set or computer, or to literally be an armchair philosopher.' A mouse in a natural environment will update its knowledge about food sources or potential dangers while interacting directly with its environment. The more the animal moves, the more it is likely to learn. 'In the course of time, the hippocampus will adapt to the amount of flexibility that is required to cope with the complexity it encounters,' Kempermann explained. According to his 'neurogenic reserve hypothesis', physical activity is a signal for neuronal precursor cells to divide and thereby prepare the hippocampus to react to new situations.

Since the rediscovery of adult neurogenesis in the mammalian hippocampus, researchers have focused their attention on understanding the function of these new neurons. The correlation between learning and cell survival works in both directions, in that those cells in the

hippocampus are required for learning to take place—at least for specific types of learning. The first evidence for this came from Shors and Gould in 2001. They treated rats with the toxin methylazoxymethanol acetate, which reduces the number of newly generated cells in the hippocampus. This impaired specific kinds of learning, like eyeblink conditioning and trace fear conditioning [5]. A number of subsequent studies using different techniques to eliminate or reduce adult hippocampal neurogenesis drew similar conclusions. It seems that hippocampal neurogenesis is required for several learning paradigms, among them spatial learning and, importantly, ‘pattern separation’. Conversely, manipulations that increased neurogenesis improved memory resolution and facilitated pattern separation.

In simple terms, pattern separation is the ability to develop unique memory traces for similar events. Kempermann gave the example of parking a car in a large car park every day and keeping track of where it is located. “New cells in the hippocampus are required to flexibly integrate new information into existing knowledge,” he said. “Past information does not have to be overwritten. There is no need to forget where you parked the car 3 days ago. But the map has to be updated with information about the car’s current location.” As a rule, neurons in the hippocampus do not fire very often; they are strongly tuned to specific kinds of memory. But new neurons are, in this respect, different. They are far more excitable. They are not as specialized as their older counterparts and therefore much more prone to learning. “Essentially all of the plasticity in the hippocampal dentate gyrus comes from the new cells,” Kempermann explained.

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“The ability to integrate new information is impaired very early in Alzheimer disease,” Kempermann explained. “People have problems with novelty.” For example, people living with Alzheimer disease are increasingly unable to distinguish between highly similar memories: today’s breakfast from

yesterday’s breakfast, or the corridor on the second floor from the corridor on the third floor. These problems are probably caused by a lack of newly generated cells in the hippocampus.

The production of senile plaques—aggregated amyloid-beta peptides cleaved from the amyloid precursor protein (APP)—is the pathological hallmark of Alzheimer disease and a major cause for neuronal cell death in the brain. In addition, there are several indications that APP cleavage may also directly impact hippocampal neurogenesis. For example, the expression of APP intracellular domain (AICD), the intracellular product of amylogenic cleavage of APP, hinders hippocampal cell proliferation and survival. In contrast, sAPP α , a product of healthy APP cleavage, stimulates neurogenesis and protects neuronal survival in the hippocampus. Moreover, hippocampal proliferation was found to be strongly reduced in a mouse model of Alzheimer disease long before any deposition of amyloid peptides could be detected. Impaired hippocampal neurogenesis might therefore be one of the earliest events in the development of Alzheimer disease. Countering this impairment—for example by exercising—could therefore be particularly effective in delaying the onset of the first symptoms. “If we could delay the onset of the disease for a couple of years, we would achieve a lot,” Kempermann said. Considering the fact that there is, as yet, no cure for the disease, delaying its onset is currently the most promising strategy to reduce its prevalence.

Animal studies provide clear evidence that exercising induces neurogenesis in the hippocampus, but does this also apply in humans? “Unfortunately, we have no means of knowing,” said Kirsten Hötting, a neuropsychologist at the University of Hamburg in Germany. “With imaging methods like MRI, we do not have the resolution to look at single cells. We are working at an entirely different scale.” Nonetheless, there is indirect evidence in humans that exercise boosts hippocampal neurogenesis—either proliferation or neuronal growth. Arthur Kramer from the University of Illinois, USA, and his colleagues have demonstrated that aerobic exercise increases the size of the hippocampus and improves spatial memory [6]. In addition, increased hippocampal volume was found to be associated with higher serum levels of brain-derived neurotrophic factor (BDNF), which has been shown to

induce hippocampal cell proliferation and survival in response to physical activity in rodents. But hippocampal growth is certainly not the only effect of sport. “We do see effects on the brain outside the hippocampus,” Hötting said.

Animal studies have shown that a combination of physical and mental training is most effective in increasing the number of newly generated cells in the hippocampus. It is thus conceivable that a combination of sport and mental training might well have an additive effect on cognitive function in humans. Although there are only a few studies that have investigated this question, they are nonetheless encouraging. One study evaluating the effects of different forms of training in 375 community residents aged 75–93 years over 5 years showed that combined cognitive and physical training had the largest impact on several measures, including cognitive status [7]. More recently, Hötting and her colleagues investigated the effect of endurance training and cognitive training on spatial orientation—a task that is strongly dependent on the hippocampus [8]. They found that physical fitness correlated with changes in neuronal activity in brain regions associated with spatial learning, but only if subjects had additional spatial training. “Sports may generally prepare the brain to better react to specific cognitive challenges, but additional cognitive training is required,” Hötting concluded, confirming Kempermann’s results from animal studies.

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The idea can even be taken a step further. If both mental and physical activity are required to improve cognition, would it make sense to combine the two in a form of exercise that is also mentally challenging? Shors and her colleagues tested this idea in rats. Because the usual animal learning paradigms, such as eyeblink conditioning, are trickier to extrapolate to humans, Shors had the animals learn a complex physical skill in the

same way that humans master various physical skills over a lifetime. “We wanted the rats to learn something that was more human-like,” Shors explained. In this case, the skill was balancing on a rod that was turning at accelerating speed. The researchers found that cell survival in the hippocampus was greatly increased in rats that successfully acquired the skill, in contrast to animals that did not master the task [9]. This result may seem counterintuitive, because physical skill learning does not depend on the hippocampus. However, as Shors explained, “the fact that the task does not depend on the hippocampus does not mean that the hippocampus is not involved. [...] The hippocampus is nonetheless active and responds during learning experiences. When you are learning something, it is more than just the task that is important. It is also when and where it happens, the context of learning, and how it relates to other experiences in the past. All these aspects of the experience are integrated in the hippocampus so that the information can be used to express adaptive thoughts and behavioral responses in the future.”

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Studies in humans also show that learning a physical skill—dancing, in this case—can slow cognitive decline. Joe Verghese and his colleagues at the Albert Einstein College of Medicine (New York, USA) investigated how different leisure activities impact on the risk of dementia [10]. They found that reading, playing board games, and playing musical instruments were all associated with a reduced risk of dementia. But of all activities, dancing had the strongest effect. Hubert

Dinse and coworkers at the Ruhr-University Bochum, Germany, have also found that dancing improves cognitive performance in the elderly. Even in a training program lasting only 6 months—during which elderly subjects were trained in increasingly more complex step sequences once a week—the subjects’ cognitive abilities were considerably improved [11].

With the demographic change toward ageing populations in many Western countries, Alzheimer disease is becoming a major challenge for society. Researchers are striving to find cures, but no effective pharmacological treatments are yet available. The search for preventive strategies has therefore gained momentum, as a lot could be gained by delaying disease onset for just a few years.

A decrease in adult hippocampal neurogenesis is probably a major cause for age-related cognitive decline. But there may be ways to counteract this impairment. Animal studies suggest that exercising increases the proliferation of hippocampal neurons and that learning is required to keep these cells alive. In fact, combining physical and mental activity yields a greater increase in new hippocampal neurons than either stimulus alone. Preliminary studies show that these results may also be extrapolated to humans. A combination of exercising and mental activity has been shown to be most effective in preventing cognitive decline. Dancing—which is in itself physically and mentally challenging—may be a good measure to keep the brain fit and help prevent Alzheimer disease.

Conflict of interest

The author declares that she has no conflict of interest.

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