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“Prevention is Better than Cure”: Can Exercise Prevent Dementia?

Review

Neurodegenerative disorders such as dementia are among the ones for which no cure is found yet. Nevertheless, physical exercise in older adults has shown to be beneficial for enhancement of cognitive functions such as memory and learning. The underlying mechanism of these beneficial effects is suggested to be neurogenesis in the dentate gyrus in the hippocampus, a brain structure essential for memory function. It is suggested that physical exercise and therewith neurogenesis can work as preventing factors for dementia. This paper examines whether physical exercise can prevent dementia. Despite the evidence for improvement of cognitive functioning and neurogenesis after physical exercise, this paper highlights a gap of knowledge in this field with regards to evidence and research on neurogenesis in humans.

Keywords: Dementia, physical exercise, memory, neurogenesis, hippocampus

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INTRODUCTION

Dementia is a debilitating disorder, affecting many of the elderly population, and notwithstanding the progress science makes, there is no cure found yet. Dementia displays a set of symptoms that most commonly include memory loss, but also social and emotional difficulties, and other cognitive and functional declines. There are different subtypes of dementia of which the most common is Alzheimer's disease (AD) with a prevalence of about 70% in all dementia cases (Forbes et al., 2015). In the brain, AD is characterized by brain atrophy (loss of cells and cortical volume) especially in the hippocampus, extracellular deposition of amyloid-β plaques and neurofibrillary tangles of protein tau (Dubois et al., 2010). According to the World Alzheimer Report 2015 (Batsch & Mittelman, 2015), in 2050 there will be 131.5 million people in the world diagnosed with dementia. In addition to the alarming increase of the prevalence of AD and therewith dementia, the global costs of dementia, which keep increasing due to the increasing prevalence, cause concern. There is no doubt that dementia is one of the biggest global public health and social (care) challenges to date and therefore the need for a cure is high. However, while there is being looked into the possibilities for a cure, one should not forget that prevention is better than cure, and the possibilities for prevention should be investigated.

Having highlighted the importance for a treatment or prevention of dementia, one can start looking into what has already been done towards this matter. Much has been attempted in order to find a measure that prevents or delays the onset of dementia. For instance selective estrogen receptors have been examined; it has been hypothesized that the decline in estrogen levels following menopause increases the risk of AD in older women (35 – 80 years old, mean age 66) and selective estrogen agonists can reduce this risk (Yaffe et al., 2014). Additionally, omega-3 fatty acids and red-wine derived polyphenols have been studied with regards to their

protective effects against AD (Pasinetti, 2012; Sydenham, Dangour, & Lim, 2012). Even aspirin or anti-inflammatory drugs can slow down or prevent the inflammatory processes which takes place in the pathogenesis of dementia, thus preventing or postponing the onset of the disease (Jordan et al., 2015). To date, none of these studies has been able to demonstrate any particularly strong links between the mentioned interventions and prevention or delay of dementia.

Nonetheless, studies have identified physical activity as an effective factor in improving the symptoms of dementia, delaying its onset or slowing down its progression (Chen, Zhang, & Huang, 2016; Forbes et al., 2015). It is suggested that the underlying mechanism of the dementia delaying effect is neurogenesis in the hippocampus (Jacotte-Simancas et al., 2015; Yau, Gil-Mohapel, Christie, & So, 2014). Hippocampal neurogenesis is a continuous production of new neurons in the hippocampal dentate gyrus, a brain region that plays an important role in learning and the formation of memories. Animal studies have shown that physical exercise (PE) can induce hippocampal neurogenesis (Inoue et al., 2015; Sakurai et al., 2012; Van Praag, Christie, Sejnowski, & Gage, 1999a). However, this raises the question whether these results are translatable to humans. To give an account for the possibilities of the translatability, this paper will look into whether there is convincing evidence that PE induces hippocampal neurogenesis in humans and whether this can help preventing dementia.

PHYSICAL EXERCISE AND NEUROGENESIS

Recent research has found that physical exercise has beneficial effects on cognitive functioning in older adults (60 years or older) (Carlson et al., 2008; Carvalho, Rea, Parimon, & Cusack, 2014; Sánchez-Horcajo, Llamas-Alonso, & Cimadevilla, 2015). There is evidence for better spatial memory in humans when PE is a habitual activity (Sánchez-Horcajo et al., 2015). In addition, studies reported improved memory function, executive function and other cognitive functions

in older adults (60 years and older) after six months or more of physical activity (Carlson et al., 2008; Carvalho et al., 2014; Kramer et al., 1999). Additionally, improved object recognition was reported in rats after 20 days of physical activity (Jacotte-Simancas et al., 2015). Despite the apparent cognition enhancing effect of PE, the underlying mechanism is not entirely clear. It is suggested that the production of new neurons (neurogenesis) in the hippocampus plays a critical role herein (Inoue et al., 2015; Jacotte-Simancas et al., 2015; Yau et al., 2014). This hypothesis is supported by animal studies that have shown that neurogenesis in adult mice can be enhanced by PE (Van Praag et al., 1999a; Van Praag, Kempermann, & Gage, 1999c). Mice were housed either with or without a running wheel and injected with bromodeoxyuridine (BrdU) to label dividing cells in the hippocampus. Results showed that the mice living with the running wheel displayed an increased number of BrdU-positive cells and enhanced dentate gyrus LTP. In addition, this study showed that running enhances spatial learning in mice as shown by better performance on the water maze task by the 'running wheel mice' compared to the controls (Van Praag et al., 1999a). This has also been found in AD models of mice (Adlard, Perreau, Pop, & Cotman, 2005), genetically modified mice to mimic AD pathologies, even after onset of AD pathology (Nichol, Parachikova, & Cotman, 2007). However, the results with regards to spatial learning remain arbitrary since other studies report no benefits of PE on it (Cracchiolo et al., 2007; Wolf et al., 2006). Additionally, this enhanced spatial learning effect is only present when physical activity is mild and continues over a longer period of time as opposed to intense exercise, as shown by a six-week treadmill running training (forced exercise) rat model (Inoue et al., 2015). This seems to be linked to an increased stress reaction to intense running as opposed to mild intensity running. Also, it should be taken into account that BrdU labeling and post-injection survival times of these labels can vary (Van Praag, 2008).

Exploring human adult neurogenesis in vivo remains a challenge due to technical limitations (Yau et al., 2014). Nevertheless, exercise-induced neurogenesis in humans is explored. For instance, a fMRI study showed that three months of PE correlates with increased

BOLD levels in the dentate gyrus as well as with an improvement in cognitive function scores (Pereira et al., 2007; Reinsberger, 2015). Given the fact that the dentate gyrus is the only hippocampal region that supports neurogenesis in the adult brain (Eriksson et al., 1998), it can be speculated that the exercise-induced BOLD response is a result of exercise-induced neurogenesis. However, until other possible sources for this increased BOLD response can be excluded, this remains a speculation. Another study using high-resolution MRI scans in 55 older adults (55 years or older, with mean age 66.5) showed that higher aerobic fitness as indicated by maximal oxygen uptake (VO_2) reduced the loss of cortical volume (Colcombe et al., 2003). The results of these studies suggest that fMRI can be a promising tool to examine relations between PE and dementia related brain decline. With regards to neurogenesis in vivo measures in humans, these findings are preliminary until more and especially more direct measures of human neurogenesis are available.

Together, the currently available evidence points towards an association between PE and hippocampal neurogenesis in humans as well as in animals, indicating that adult hippocampal neurogenesis may be the underlying cause of enhanced performance and therewith be involved in learning and memory in the human brain. Nevertheless, without the technical means to explore this specifically in humans, this remains an area for further work and one should be cautious with drawing conclusions.

EXERCISE, NEUROGENESIS AND DEMENTIA PREVENTION

The next step is fitting in the aforementioned results with prevention of dementia. What is the relevance of exercise-induced hippocampal neurogenesis in prevention of dementia? In recent years, there has been an increasing amount of studies on the relevance of exercise in preventing dementia or at least lowering the risks or symptom severity (Elwood et al., 2013; Forbes et al., 2015; Taaffe et al., 2008; Yau et al., 2014).

For instance, it is shown that men who exercised regularly or who had higher levels of PE, had a lower risk of dementia and the lowest compared to other healthy lifestyle factors such as healthy diet, weight, etc. (Elwood et al., 2013; Taaffe et al., 2008). Healthy behaviors were recorded on 2235 men aged 45-59 years for 30 years during which disease and death were recorded, and after which cognitive state was determined (Elwood et al., 2013). In the other study, physical activity was assessed in 2263 men aged 71-92 years and repeated examinations for dementia were conducted as follow-up after 3 and 6 years (Taaffe et al., 2008). The incidence of dementia significantly decreased with increasing physical activity (Taaffe et al., 2008), whereas there was no significant decrease of dementia incidence after having a healthy lifestyle (Elwood et al., 2013). However, these effects of PE were only found in men with low physical function, similar associations were absent in men with high physical function. While this a step forward, this study should be repeated with different samples to examine whether this effect is present in other populations.

Besides the evidence on the decreased risk of acquiring dementia after PE, there is also evidence on beneficial effects of PE on brain related characteristics of dementia. For instance, it has been shown that physical activity can reduce brain atrophy (Colcombe et al., 2003), one of the hallmarks of dementia. Additionally, it has been found that five months of voluntary exercise decreased extracellular amyloid-β plaques in the frontal cortex and hippocampus in an AD model of mice (Adlard et al., 2005).

If the knowledge that is found throughout the literature is combined, one can conclude that there is no doubt about the memory and learning enhancing effects of PE. Additionally, there is support for the fact that PE induces neurogenesis in the animal and human brain. However, if the debate is to be moved forward, a better understanding of neurogenesis and its preventive power in dementia needs to be developed and especially the means to investigate this in humans.

DISCUSSION

Physical exercise has shown to be one of the most effective and low-cost ways for successful ageing and therefore it has the potential to be a preventive or disease-slowing therapeutic strategy for age-related neurodegenerative disorders like dementia. The in this paper described studies have provided evidence for the fact that PE improves memory and learning in older adults and that it decreases the risk for dementia. However, despite the strong evidence for the cognitive enhancing effects of physical activity in elderly persons, challenges in the research into neurogenesis in human brains in vivo remain. The examined literature suggests that PE has beneficial effects on memory, learning and the increase of neurogenesis, however for the implications in preventing dementia there is more research needed.

Nevertheless, even though it remains unknown whether dementia can be delayed or prevented, and whether neurogenesis lies at the core of this, cognitive and memory functioning can be improved with physical activity. Even when taking into account the decreasing physical abilities of elderly people, there are plenty of possibilities for them to be physically active. As such, walking seems already to be beneficial for memory and other executive functions (Abbott et al., 2004; Scherder et al., 2014). Additionally, a study reports that older adults who have been dancing for multiple years seem to show superior cognitive performance in comparison to their age-matched sedentary controls (Kattenstroth, Kolankowska, Kalisch, & Dinse, 2010). This

might also be the case for other physical activities that have been performed for several years in later age.

Despite the lack of evidence that could lead us to say that PE induces neurogenesis which could possibly prevent dementia, this field provides a fruitful area for further work. For instance, recent developments in imaging techniques are getting closer to in vivo imaging of neurogenesis with MRI in humans. As such, multimodal neuroimaging studies are suggested, which use different imaging techniques to assess brain structure and function within the same individual (Ho, Hooker, Sahay, Holt, & Roffman, 2013). This way, microscopic dynamics of adult hippocampal neurogenesis can be understood with macroscopic imaging methods, and weaknesses of individual imaging methods are mitigated. Further, methods that have been specifically designed to detect neurogenesis in vivo in humans are MRI based cerebral blood volume measurements and spectroscopic biomarkers (Sierra, Encinas, & Maletic-Savatic, 2011). In the latter, magnetic properties of different protons are exploited with MRI.

Additionally, evidence from Traumatic Brain Injury (TBI) research can be valuable in integrating the power of neurogenesis with preventing dementia. As such, it is reported that PE reduces memory deficits after TBI in animals (Griesbach, Hovda, Molteni, Wu, & Gomez-Pinilla, 2004), which could point towards the same effect in dementia-related memory deficits. The reduced deficits seem to be mediated by amongst others angiogenesis, a process through which new blood vessels form from pre-existing vessels, cell proliferation and neurogenesis (Griesbach, Hovda, & Gomez-Pinilla, 2009). Together, these advances will most likely contribute to our understanding of the relationship between PE, neurogenesis and its potential protective effects regarding dementia. Lastly, it is vital to investigate whether hippocampal neurogenesis really prevents dementia or whether it just circumvents the most pronounced symptom, namely memory loss, as well as the question whether dementia can be truly prevented or whether it will only be possible to delay its onset.

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