

Can neuroplasticity induced by physical exercise play a positive action in Parkinson's disease?

Pode a neuroplasticidade induzida pelo exercício físico desempenhar ação positiva na doença de Parkinson?

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ABSTRACT

Introduction: Parkinson's disease (PD) is a neurodegenerative, chronic and progressive disease with impaired motor and non-motor function, whose progression leads to instability.

Objective: To verify the correlation between physical activity and neuroplasticity in people with PD.

Method: This is a systematic review of the literature using the PubMed and ScienceDirect databases. The selected articles corresponded to the period from 2013 to 2023, through the descriptors "exercise-induced neuroplasticity", "neuronal plasticity" and "Parkinson's disease".

Result: Most of the selected studies showed improvement in motor complaints, as well as favorable results in increasing neuroplasticity with the practice of physical exercises. Performing intense physical activity increases dopamine D2 levels and improves postural control in the early stages, and intense aerobic exercise increases serum BDNF levels, a factor previously associated with motor changes in PD.

Conclusion: Although there are few studies involving humans, important associations have been observed in which brain functionality and structure are modulated by physical activity. In this sense, behavioral, motor and cognitive symptoms related to PD improve through increased dopaminergic levels

KEYWORDS: Exercise-induced neuroplasticity. Neuronal plasticity. Parkinson's disease.

Central Message

Exercise-induced neuroplasticity is a promising topic in the treatment of Parkinson's disease. This review explores the neurobiological mechanisms involved and the potential benefits of this therapeutic approach, highlighting its clinical and scientific relevance.

Perspective

Intense physical activity generates an increase in dopamine D2 levels and improve postural control in patients with Parkinson's in the early stages, and intense aerobic exercises can generate an increase in serum BDNF levels, a factor previously associated with the motor alterations of the disease.

RESUMO

Introdução: Doença de Parkinson (DP) é neurodegenerativa, de caráter crônico e progressivo com comprometimento da função motora e não motora, cuja evolução leva à instabilidades.

Objetivo: Verificar a correlação da prática de atividade física e a neuroplasticidade em pessoas com DP.

Método: Trata-se de revisão sistemática da literatura utilizando as bases de dados PubMed e ScienceDirect. Os artigos selecionados corresponderam ao período de 2013 a 2023, por meio dos descritores "exercise-induced neuroplasticity", "neuronal plasticity" e "Parkinson's disease".

Resultado: Em sua maioria, os estudos selecionados evidenciaram melhora das queixas motoras, assim como, resultados favoráveis ao aumento da neuroplasticidade com a prática de exercícios físicos. A realização de atividade física intensa gera elevação dos níveis de dopamina D2 e melhora do controle postural em estágios iniciais, e exercícios aeróbicos intensos geram aumento nos níveis séricos de BDNF, fator previamente associado à alterações motoras da DP.

Conclusão: Embora existam poucos estudos envolvendo seres humanos, observou-se importantes associações, nas quais a funcionalidade e a estrutura cerebral são moduladas pela atividade física. Nesse sentido, melhoram os sintomas comportamentais, motores e cognitivos relacionados à DP, mediante elevação de níveis dopaminérgicos.

PALAVRAS-CHAVE: Doença de Parkinson. Neuroplasticidade induzida pelo exercício. Plasticidade neuronal.

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease, resulting from the loss of dopaminergic neurons in the substantia nigra, of a chronic and progressive nature, presenting with impairment of motor and non-motor function.¹

It is a heterogeneous disease, resulting from phenotypic variability and its nature is progressive.² With evolution, there is also a severe progression of instability and motor disorders.³ Thus, the association of physical practice in patients with PD has been studied, due to the neuroprotective mechanisms offered by this activity.²

There is little knowledge about neuroplastic modulations induced by physical exercise. However, according to the literature, patients who underwent intensive rehabilitation showed increased dopamine, receptor density and better postural control, a fact that corroborates the theory of the relationship between neuroplastic mechanisms positively influencing neurodegenerative diseases such as PD.^{1,2}

The aim of this review was to understand the role of exercise-induced neuroplastic modulation and to establish current evidence of the correlation between physical activity and neuroplasticity in people with PD.

METHOD

This is a systematic review of the literature, which searched through the DeCS/MeSH descriptors "exercise-induced neuroplasticity", "neuronal plasticity" and "Parkinson's disease" intersected with the Boolean operators "AND" and "OR", for the search in the PubMed and ScienceDirect databases in the period from 2012 to 2023. A total of 378 articles were found, according to the inclusion criteria, period of publication, free text in full and relevant aspects of the guiding question, and in the end 78 articles were analyzed, of which 10 were selected to compose the present review (Figure).

The sample consisted of 10 articles 1-10, published between 2012 and 2023, 1 in 2012, 1 in 2013, 1 in 2014, 2 in 2016, 1 in 2017, 1 in 2020, 2 in 2022, 1 in 2023, all of which were in English. Other characteristics of the studies are shown in Table 1.

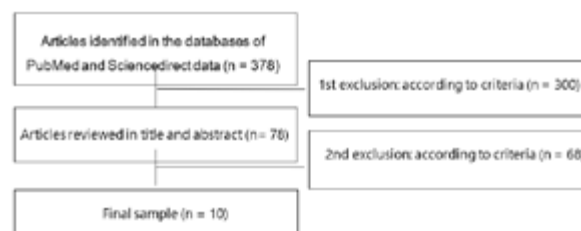


FIGURE — Flowchart for the selection of studies.

To assess the correlation between physical exercise and neuroplasticity in PD, the 10 studies 1-10 were presented in Table 2, which highlights the objectives and results of the evaluations according to authorship and year of publication.

In the analysis of the results obtained from the sample, it was observed both in the animal model and in studies in humans with PD, favorable changes in brain function and structure after a period of exercise, improvement in motor symptoms, as well as validation of the correlation between neuroplasticity after a period of physical exercise.

DISCUSSION

The practice of physical activity, in a continuous practical way, and participation in competitive sports during youth are associated with a lower risk of PD in adulthood. More recent studies show that intense physical activity increases dopamine D2 levels and improves postural control in early stages, and intense aerobic exercises generate an increase in serum BDNF levels, a factor previously associated with PD motor changes. Even though it is already established that neuroplasticity is modulated by exercise through BDNF, the pathophysiology of this pathway is unknown, even without a complete notion of whether physical exercise leads to neuroprotective or neurodegenerative properties.⁴

In general, studies have shown positive effects of physical activity on neuroplasticity; however, the biochemical pathways through which such effects are obtained still need more in-depth studies for better understanding. This review showed that both brain function and structure improved in patients with idiopathic PD after a period of physical activity. However, the neurochemical adaptation of the brain to exercise had mixed results, with no improvement

TABLE 1 — Characterization of studies according to authorship, year of publication, journal, language and object of study 1-10

Authorship/Year of Publication	Journal and language	Object of Study
Hirsch MA et al. 2016 ⁴	Parkinsonism Relat Disord English	8 studies with 144 adults with PD of varying severity
Liu HH et al. 2022 ⁵	Geriatr Nurs English	28 individuals with PD, 14 of whom were in the experimental group and 14 in the control group
Nicolini C et al. 2020 ⁷	Neuroscience English	05 studies on different exercise protocols in physically active or sedentary young adults, healthy.
Petzinger GM et al. 2013 ⁸	Lancet Neurol English	Studies published in human beings and animal models of PD
Ridgel AL et al. 2012 ³	Arch Phys Med Rehabil English	10 subjects with idiopathic PD, including 4 males and 6 females
Shih IF et al. 2016 ⁵	Parkinsonism Relat Disord English	357 incident cases of PD and 341 controls
Tsai CL et al. 2023 ⁹	Mental Health and Physical Activity English	23 participants with mild to moderate PD
Vitorino LC et al. 2022 ¹⁰	Neurosci Lett English	40 male Swiss mice, determined in: sedentary control (n = 10), exercise control (n = 10), sedentary Parkinson's (n = 10) and exercise (n = 10).
Wang Z et al. 2014 ¹	Neurobiol Aging English	3-month-old male Sprague-Dawley rats, divided into: injury/exercise (n = 1/412), injury/no exercise (n = 1/410) and simulated/exercise (n = 1/49)
Watson JW et al. 2017 ²	Academic Press English	Compiled from molecular-level and systems-level research in animal models and human studies.

TABLE 2 – Description of the objective and results of the sample according to authorship. 1-10

Authorship/Year of Publication	Goal	Findings
Hirsch MA et al. 2016 ⁴	To present 8 studies of PD in humans on the effects of physical and cognitive activity on brain structure or function in PD.	Exercise triggers events related to neuroplasticity in people with PD, such as corticomotor excitation, increases and decreases in gray matter volume, and changes in BDNF levels.
Liu HH et al. 2022 ⁶	To investigate the effects of step-in-square (SSE) exercise on executive function in people with Parkinson's disease (PD)	Improvements to executive function in digit range tasks and track testing after SSE training. In participants with mild cognitive impairment (MCI), better performance in executive function and global cognition was observed, as measured by the Montreal cognitive assessment.
Nicolini C et al. 2020 ⁷	To review results from studies that investigated neurophysiological and molecular changes associated with acute or long-term exercise in audible young adults and in healthy postmenopausal women.	Mediators of positive effects of high-intensity exercise on motor behavior increase cortical excitability and BDNF, both modulators of neuroplasticity.
Petzinger GM et al. 2013 ⁸	To highlight studies published in humans and animal models of PD that point to the beneficial effects of exercise through neuroplasticity.	Goal-based training with aerobic training can work in tandem to promote automatic and volitional components of motor control.
Ridgel AL et al. 2012 ³	To develop a Rapid Cadence Cycling or Active Assisted Cycling (AAC) intervention in individuals with PD and to investigate the results in tremors and bradykinesia in a single session of AAC at high cadence.	CAA was well tolerated by individuals with PD and 78% of the participants showed improvement in motor function, tremor and bradykinesia immediately after a cycling session.
Shih IF et al. 2016 ⁵	To examine the type and/or timing of physical activity performed during adulthood and its influence on future risk of PD.	The risks of PD were lower and 44% of the participants who practiced moderate to vigorous physical activity (PA) in the period between 18 and 24 years of age, when compared to the less active group. The same was not observed in the period aged between 25 and 44 years. Individuals who practiced PA constantly at high levels (< 65 years of age) had a 51% lower risk of PD than those with low levels. In addition, having participated in competitive sports before the age of 25 was inversely associated with PD.
Tsai CL et al. 2023 ⁹	To analyze the acute effects of high-intensity interval exercise (HIIE) and moderate-intensity continuous exercise (EMIMC) on neurocognitive performance and neurotransmitter levels of individuals with D.P.	For individuals with mild to moderate PD, acute HIIE and EMIMC have been shown to be tolerable, safe, and effective modes of aerobic exercise, although the acute benefits of the exercises studied appear to be dependent on intensity.
Vitorino LC et al. 2022 ¹⁰	To investigate the effects of treadmill training on astrocytes and strials in a PD undongo cam model by combining immunohistochemistry and western-blotting for glial fibril acid protein (GFAP) with morphometric analyses.	Physical exercise had neuromodulatory effects on astrocytes. Compared to the control groups, the mice of the Parkins on Sedentary (SEDPD) group showed reactive astroglisis of these cells, showing that exercise constitutes an external stimulus capable of modulating the characteristics of glial cells.
Wang Z et al. 2014 ¹	To characterize changes in resting-state functional connectivity (rsFC) in a model of parkinsonism in rats with intra-striatal 6-hydroxy dopamine (6-OHDA) injury and to outline the effects of long-term aerobic training on rsFC, focusing on the motor circuitry.	Exercise in injured rats resulted in: normalization of injury-induced changes in RSFC; emergence of the ventrolateral striatum; and increased rsFC between the ex motor cortex, motor thalamus, basal ganglia, and cerebellum. Therefore, long-term physical training partially reviewed the changes caused by injury in the rsFC of motor circuits and improved functional connectivity in motor pathways in parkinsonian rats.
Watson JW et al. 2017 ²	To present current scientific evidence of the influence of physical activity and exercise on muscle function and associated brain changes in the parkinsonian brain	The neuroplastic alterations observed are: alterations in the transmission of dopamine and glutamate in the basal ganglia pathways; increase in neurotrophic factors; changes in function and structure in and out of the brain network affected by PD.

effect in some studies.⁵

Most of the understanding of possible benefits of physical activity in PD has been demonstrated only in animal models. In these models, it was demonstrated that some exercises, especially those performed under conditions of high arousal, led to positive changes in brain architecture and function due to the neuroplasticity, neuroprotection, and neurorestoration involved in performing physical activities. So far, better results have been demonstrated in younger patients, and many human studies have major limitations, such as small numbers of participants.¹

Neurotrophins such as BDNF can be interesting markers to relate to neuroplasticity or exercise-induced outcomes; however, it is still important to understand the association between serum BDNF levels and degree of physical activity, pharmacological interventions, among others, since this factor has many immeasurable variables.¹

Exercise-induced neuroplasticity generates improvements in cognitive and motor functions, reduction of behavioral symptoms, such as tremor in PD, even in young people without comorbidities, and significant improvement has been demonstrated in patients with PD. High-intensity exercise generates more intense and long-lasting neuroplasticity, with great improvements in motor and cognitive functions, or slowing the progression of existing neurological diseases. It was demonstrated that both aerobic and resistance exercises, when performed at high intensity, improved markers of neuroplasticity.²

Exercise is a promising and cost-effective intervention to support successful aging and

neurorehabilitation, in cases, for example, of PD.⁶ The decline in gray and white matter accompanies the physiological aging process and contributes to motor deficits in the elderly. Exercise is thought to reduce motor system atrophy and induce neuroplasticity, which in turn helps preserve motor function during aging and promotes the learning of motor skills, such as after stroke.⁶

Exercise-based interventions for people with PD include specific motor skills training to activate cognitive circuits important for motor learning. In this exercise approach, physical therapy supports learning through guidance and biofeedback.⁶

People with PD become more cognitively involved in practicing and learning movements and skills that were previously automatic and unconscious. Aerobic exercise, thought to be important for improving circulation and promoting neuroplasticity in older adults, may also play a role in improving behavioral function in people with PD.⁶ Exercise that incorporates goal-directed training and aerobic activity has the potential to improve cognitive and automatic components of motor control in individuals with mild to moderate disease through experience-dependent neuroplasticity.⁷

To fully reap the benefits of exercise training, it is critical to better understand the neurophysiological and molecular mechanisms underlying the brain changes triggered by exercise training that promote neuroplasticity and therefore help delay, decrease, and improve age- and disease-related impairments of motor function. This knowledge will enable us to develop more effective and personalized training

protocols that cater to individual needs, thereby increasing the usefulness of training strategies in both clinical and non-clinical settings.⁷

A study carried out in 2022 compared 40 mice separated between control and PD groups that were sedentary and performed physical activity.⁸ An increase in glial fibrillary acid protein was observed in striatal astrocytes in PD mice that performed physical activity when compared to sedentary mice.⁸ In addition, the same study found that in the group of rats with PD practicing physical activity, there was an increase in primary and secondary astrocyte processes and a reduction in the width of the primary processes, indicating that the morphology of the astrocytes in the sample with PD became closer to the basal astrocyte morphology of rats without PD - that is, there was neuroplasticity of these structures promoted by physical activity.⁸

Researchers in Taiwan compared 23 patients diagnosed with mild and moderate PD after high-intensity interval exercise and moderate-intensity continuous exercise through laboratory tests and memory tests before and shortly after physical activities.⁹ This research concluded that both activities promoted faster RTs and P3 ERP waves with higher amplitudes, that is, improved cognitive performance.⁹ The authors further suggested that both exercises may slow cognitive decline.⁹ However, in the biochemical aspect, only in moderate continuous exercise there was an increase in dopamine levels.⁹

Another study in Taiwan, in 2022, analyzed the effects of Square Stepping Exercise (SSE) on the executive function of patients with PD.¹⁰ SSE is a type of exercise that originated in Japan, in which participants need to memorize sequences of multidirectional steps, thus exercising the practitioners' memory, attention, and executive function skills.¹⁰ The study analyzed 28 patients, divided into 14 controls and 14 with PD, applying several tests before and after SSE.¹⁰ After 8 weeks of SSE 2 times a week, the study concluded that there was a significant improvement in the executive function of these patients in the digit span and track tests.¹⁰ In addition, the authors observed that those with mild cognitive impairment obtained improvement not only in executive function, but also in global cognition through the Montreal cognitive assessment, demonstrating the benefits of such activity in PD patients.¹⁰

CONCLUSION

Although there are few studies involving human beings, important associations have been observed in which both brain function and structure improve in PD patients after a period of physical activity, in which high-intensity activities generate more intense and lasting effects, reduce behavioral symptoms

such as tremor and improve cognitive and motor functions. Continuous activity of medium intensity raises dopamine levels. In addition, there is a need for more in-depth studies to understand the biochemical pathways of neuroplasticity resulting from physical activities in patients with PD, seeking to know its neurophysiological and molecular mechanisms when evaluated with the use of markers such as neurotrophin BDNF. The importance of this knowledge will enable us to develop more effective and personalized training protocols that meet individual needs, thereby increasing the usefulness of training strategies in both clinical and non-clinical settings.

Authors' contributions

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Formal analysis: Gustavo Rassier Isolan

Methodology: Rafaela Fernandes Gonçalves

Writing (original draft): All authors

Writing (proofreading and editing): All authors

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