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Enhancing both motor and cognitive functioning in Parkinson's disease: Aerobic exercise as a rehabilitative intervention

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ABSTRACT

Background: Aerobic exercise training (AET) has been shown to provide health benefits in individuals with Parkinson's disease (PD). However, it is yet unknown to what extent AET also improves cognitive and procedural learning capacities, which ensure an optimal daily functioning. *Objective:* In the current study, we assessed the effects of a 3-month AET program on executive functions (EF), implicit motor sequence learning (MSL) capacity, as well as on different health-related outcome indicators. *Methods:* Twenty healthy controls (HC) and 19 early PD individuals participated in a supervised, high-intensity, stationary recumbent bike-training program (3 times/week for 12 weeks). Exercise prescription started at 20 min (+5 min/week up to 40 min) based on participant's maximal aerobic power. Before and after AET, EF tests assessed participants' inhibition and flexibility functions, whereas implicit MSL capacity was evaluated using a version of the Serial Reaction Time Task. *Results:* The AET program was effective as indicated by significant improvement in aerobic capacity in all participants. Most importantly, AET improved inhibition but not flexibility, and motor learning skill, in both groups. *Conclusion:* Our results suggest that AET can be a valuable non-pharmacological intervention to promote physical fitness in early PD, but also better cognitive and procedural functioning.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder, which manifests through motor symptoms including tremor, rigidity, slowness of movement (bradykinesia) and gait difficulties. Neuropathologically, PD is a multisystem disorder characterised not only by nigrostriatal dopaminergic cell loss in the basal ganglia, but also by disorders of mesocortical dopaminergic, noradrenergic, and other systems (Jellinger, 2012). These lesions lead to disruptions of motor program selection by the striatal circuitry, affecting in turn, the entire cortico-striatal system (Amano, Roemmich, Skinner, & Hass, 2013), and individuals' motor learning capacity (Stefanova, Kostic, Ziropadja, Markovic, & Ocic, 2000). In addition, there is evidence that degeneration in PD is present in multiple systems even from the onset, as it can be observed in early cognitive dysfunction, mainly in processes and tasks that require executive functions, abilities directing and coordinating the execution of human behaviours (Kudlicka, Clare, & Hindle, 2011). As a result, cognitive dysfunctions aggravate motor symptoms, and in turn compromise activities of daily living and the quality of life (Dirnberger & Jahanshahi, 2013). Overall, the heterogeneous nature of the disease raises difficulties in finding treatments to alleviate these multicomponent manifestations. Thus, much effort is devoted nowadays to researching complementary, non-pharmacological interventions, which can help improve both

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motor and cognitive symptoms of PD. Physical exercise constitutes such an alternative intervention.

Among many different types of physical exercising (e.g., resistance training, flexibility, coordination etc.), aerobic exercise training (AET) has been the most studied and has shown unequivocal health benefits across the life span (Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011), as well as in different clinical populations, such as PD. Specifically in PD, AET has been found to improve physical functioning, quality of life, and functional capacities (Ahlskog, 2011; Goodwin, Richards, Taylor, Taylor, & Campbell, 2008; Gracies, 2010; Herman, Giladi, & Hausdorff, 2009; Nadeau, Pourcher, & Corbeil, 2014; Petzinger et al., 2013; Speelman et al., 2011). For instance, progressive treadmill training has revealed mobility gains following 6 weeks of AET, resulting in improvements in both activities of daily living and quality of life in people with PD (Herman, Giladi, Gruendlinger, & Hausdorff, 2007). Another cardiorespiratory exercise study in the same population has demonstrated improvements in motor functions and bimanual dexterity after only two months of intense supervised bicycle training (Ridgel, Vitek, & Alberts, 2009). While much work has been done to show the benefits of AET on functional capacities in PD, such as gait, the evidence for such an effect on cognition and motor learning capacity is still scarce (Murray, Sacheli, Eng, & Stoessl, 2014). Furthermore, additional investigations are still needed to demonstrate that such treatment can benefit cognition and motor functioning in parallel, and to identify the underlying brain mechanisms by which AET benefit PD individuals in both areas.

There is now overwhelming evidence that the adult brain is very plastic and that this cerebral plasticity is maintained or increased through exercise in elderly and other frail populations (Bherer, Erickson, & Liu-Ambrose, 2013). The structural and functional changes produced by chronic exercise have been explained by various neurophysiological mechanisms, including the synaptic plasticity (e.g., synaptogenesis, reinforcing the existing connexions due to repeated associations between new sensory and motor experiences) and a change in dopaminergic neurotransmission (Audiffren, André, & Albinet, 2011). Given that the latter mechanisms suggest the existence of a connection between the brain circuitry involved in PD (i.e., dopaminergic) and exercise-dependent cerebral plasticity, it is conceivable that this type of non-pharmacological interventions could preserve, or help restore motor and cognitive effectiveness in PD. Nevertheless, to our knowledge, no study has investigated the effect of exercise on both procedural motor learning and executive functions in PD, despite the remarkable overlap between the neuropathology of PD, and the neuronal correlates associated with exercise dependent plasticity (Petzinger et al., 2013).

To date, physical exercise literature reports similar effects of training in healthy older adults and PD patients (Audiffren et al., 2011; Bherer et al., 2013; Murray et al., 2014). Hence, the principal aim of the present study was to investigate the effects of cardiorespiratory exercise in both PD and healthy controls (HC) on cognition and motor learning, as well as to explore these effects within each group. Specifically, we hypothesised that 3 months of progressive intense aerobic exercise training (AET) would improve significantly and in a similar fashion in both groups, hence helping to normalise PD patients' performance in: (1) aerobic capacity, (2) cognitive abilities (specifically executing functions such as inhibition and flexibility), and (3) procedural motor learning.

2. Methods

2.1. Participants

A total of 39 women and men divided into two groups (19 PD patients and 20 HC aged between 40 and 80 years old) participated in the present study. Demographic characteristics of the samples are presented in Table 1. Participants were assigned to a 3-month, supervised (i.e., with trained kinesiologists) AET program in small groups of four participants per trainer. Study inclusion criteria specific to PD individuals were the following: patients had to be classified as stage 1 or 2 according to Hoehn and Yahr's scale (Hoehn & Yahr, 1967) based upon neurological evaluation, and had to score below 35 on motor functions assessed with the United Parkinson's Disease Rating Scale (UPDRS) (Goetz et al., 2008). Study inclusion criteria for both PD and HC participants were based on screening tests for dementia. Specifically, to be eligible they needed to score 24 or more on the Mini Mental State Evaluation (Folstein, Folstein, & McHugh, 1975) or on the Montreal Cognitive Assessment (Marinus, Verbaan, & van Hilten, 2011) tests. In addition, eligible participants had to be sedentary at baseline (a score of 5 or lower on the Jackson's Questionnaire) (Jackson et al., 1990). As a result of our selection process, the two groups were matched on sex distribution, age, and years of education, in addition to cognitive and fitness levels.

2.2. Cognitive and motor assessments

2.2.1. Executive functioning

Two neuropsychological executive tests measuring inhibition and flexibility abilities were administered both before and after AET in the current study (Spreen, Strauss, & Sherman, 2006). First, participants' inhibitory aptitude was evaluated using a version of the Stroop test with three different conditions (reading, naming, and inhibition). Each of these conditions was composed of 100 stimuli (i.e., words, coloured rectangles, words in colours) printed on a 21.5 × 28 cm sheet of paper. In the reading condition, participants had to read the words (red, green, blue, and yellow) printed in black. In the naming condition, subjects needed to name the colour of the rectangles. Finally, in the interference condition, individuals were asked to name the colour of the ink in which the words were written. In the latter condition, the meaning of each word had to be ignored, as it was incongruent with the colour to name (e.g., the word "green" written in red). Second, the Trail Making test (TMT) was then used to measure subjects' flexibility functions. The test has two parts, TMT A and TMT B, administered in this order. The TMT A included numbers from 1 to 25, circled and written on a 21.5 × 28 cm sheet of paper. Participants were asked to connect with a pencil, as fast as possible, the numbers in numerical order. By contrast, TMT B included numbers from 1 to 13 and letters from A to L. This time, subjects were required to connect, as fast as possible, a number followed by a letter in numerical and alphabetic order, respectively.

Table 1
Demographics of the two groups of participants.

Variables[a]	HC (n = 20)	PD (n = 19)	p-value
Sex (male/female)	8/12	13/6	0.07[b]
Age (years)	64 (8.19)	59 (7.11)	0.06[c]
Education	15.7 (2.36)	15.05 (2.78)	0.43[c]
Fitness[d]	2.1 (1.17)	1.84 (1.26)	0.51[c]
Cognition (MMSE/ MOCA)[e]	29.18/28.56 (1.25/ 1.51)	28.4/27.21 (1.34/ 1.85)	0.275/ 0.08[c]
Depression[f]	4.8 (4.5)	10.5 (8.3)	0.01[c,*]
Anxiety [f]	2.1 (2.7)	8.6 (8.4)	0.002[c,*]
Hoehn & Yahr score	N/A	2 (0)	N/A
UPDRS total score	N/A	21.84 (6.16)	N/A
Years diagnosed	N/A	8.1 (9.12)	N/A

[a] Values represent mean (standard deviation), except for 'Sex', where values represent counts.
[b] p-value from chi-square test.
[c] p-value from ANOVA.
[d] Jackson's questionnaire assessing activity level at baseline.
[e] 5 PD and 11 HC were assessed with MMSE and 14 PD and 9 HC with MOCA.
[f] Beck depression inventory and Beck anxiety were used.