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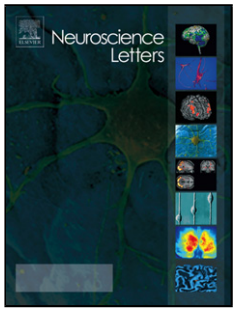

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Acute effects of aerobic exercise on cognitive function in individuals with Parkinson's disease

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Highlights

- PD patients showed no change in behaviour after an acute bout of aerobic exercise
- Improvements in behaviour in the control condition demonstrated practice effects
- Results do not support acute exercise as primer for cognitive rehabilitation in PD

Abstract

Background: Deficits in executive functions are highly prevalent in Parkinson's disease (PD). Although chronic physical exercise has been shown to improve executive functions in PD, evidence of acute exercise effects is limited. This study aimed to evaluate the effects of an acute bout of exercise on cognitive processes underlying executive functions in PD. **Methods:** Twenty individuals with PD were assessed in both a Control and an Exercise conditions. In each condition, individuals started performing a simple and a choice reaction time (RT) task. Subsequently, participants were asked to sit on a cycle ergometer (Control) or cycle (Exercise) for 20 minutes in counterbalanced order. Participants were asked to repeat both reaction time tasks after 15-minute rest period in both conditions. **Results:** While no differences were found in simple RT, participants showed faster choice RT post Exercise as well as Control conditions ($p=0.012$). Participants had slower choice RT for target stimulus compared to non-target stimuli irrespective of time or experimental condition ($p<0.001$). There was no change in accuracy following experimental conditions. **Conclusions:** Results suggest that individuals with PD may not respond behaviourally to a single bout of exercise. The lack of selective effects of exercise on cognition suggests that practice effects may have influenced previous research. Future studies

should assess whether neurophysiological changes might occur after an acute bout of exercise in PD.

Keywords: Parkinson's disease, acute exercise, cognition, reaction time

Introduction

Deficits in cognitive function have been reported as one of the main contributors to a decreased quality of life by individuals with Parkinson's disease (PD) [1]. Specifically, studies have shown that many individuals with PD experience deficits in executive functions (EF) [2]. EF deficits found in individuals with PD have been attributed to the disruption of basal ganglia-thalamo-cortical circuitries that loop through frontal lobe areas [3]. Yet, EF outcomes are variable in their response to dopaminergic treatment for nigrostriatal-related PD symptoms [4]. Therefore, complementary therapies to treat cognitive function have been investigated in PD.

A non-pharmacological therapy showing promising results in the treatment of EF deficits in PD is physical exercise. However, this growing body of literature is primarily focused on the chronic effects of exercise [5-7], while studies investigating the acute effects of exercise on cognition are almost non-existent in PD. Investigating the acute effects of exercise on cognition of individuals with PD may help understand the mechanisms underlying positive effects observed in chronic exercise interventions. Furthermore, it has been suggested that acute (transient) effects of exercise on neurophysiological markers and cognition could possibly be

used as a "primer" for subsequent rehabilitation strategies [8], for example cognitive training. Thus, determining whether acute effects of exercise on cognition exist in PD is an important step for establishing exercise as a complementary therapy in this population.

The first study to evaluate the acute effects of exercise on cognition in PD showed improvements in EF after 30 minutes of *passive* cycling [9]. Yet, a limitation of this study was the lack of a control condition in which participants did not undergo the experimental manipulation. Thus, it remains unclear whether positive results were due to passive cycling or practice effects. It is also important to note that the mechanisms underlying the effects of passive exercise on cognition are not well understood. In contrast, studies investigating the mechanisms underlying acute effects of exercise on cognition in healthy individuals have mostly used *active* exercise. In neurologically healthy young and older adults, behavioural effects following an acute bout of (*active*) exercise have been observed through decreases in reaction time (RT), especially in tasks requiring greater executive control [10, 11]. Importantly, improvements in behavioural response have been linked to changes electrophysiological measures (i.e. P300 latency and amplitude) [12] as well as greater activation of prefrontal brain areas [10, 11]. Thus, it has been argued that an acute bout of exercise may influence EF through increased frontal lobe activation. In this context, it could be hypothesized that enhanced frontal lobe activity as a result of exercise could positively influence cognitive processing through fronto-striatal loops in PD.

In the current study, three cognitive processes argued to underlie EF and be regionally organized within the frontal lobes were examined. These processes were defined as the abilities [i] to initiate and sustain a response (energization), [ii] to set a stimulus-response relationship (task-setting), and [iii] to monitor performance over time for quality control and adjustment of behaviour (monitoring) [13]. Deficits in these processes were found to contribute to impaired

performance in commonly used neuropsychological tests assessing EF such as phonemic verbal fluency, Stroop test, and the Wisconsin Card Sorting Test [14]. Most importantly, the frontal lobe areas found to be critical to each cognitive process (superior medial, left lateral, and right lateral, respectively) are known to anatomically and functionally linked to the basal ganglia [15]. Since the basal ganglia is the primary area affected in PD, it could be theorized that improvements in outcome measures representing each cognitive process could indicate enhanced information processing through fronto-striatal loops.

Thus, the aim of the present study was to investigate the effects of a single bout of *active* aerobic exercise on energization, task-setting, monitoring in PD. Given that an acute bout of exercise may enhance activity in frontal areas known to modulate these processes and that are connected to the basal ganglia, it was hypothesized that exercise would positively influence energization, task-setting, and monitoring in PD.

Methods

This study was approved by University of Waterloo and Wilfrid Laurier University research ethics boards in accordance with the Declaration of Helsinki. Informed consent was obtained from all individuals prior to participation.

Participants

Participants included 20 male and female adults (age 66.55 (10.11)) diagnosed with PD, taking appropriate medication, and with medical clearance to exercise. Participants were recruited from the database of the Movement Disorders Research and Rehabilitation Centre at Wilfrid Laurier University (Waterloo, ON, Canada). Exclusion criteria were history of

neurological diseases other than PD, unstable medical condition, uncontrolled diabetes mellitus, uncontrolled hypertension (BP>140/90), history of heart disease, resting heart rate >100, history of stroke, history of chronic obstructive pulmonary disease, or uncorrected visual impairments.

Participants completed three assessment sessions (baseline, Exercise, and Control), on three separate days, and while in their ON medication state (except for one drug naïve participant). For each participant, assessment sessions were scheduled at the same time of the day in order to control for the effect of symptoms fluctuation on participants' performance. A cross-over design was implemented, where participants performed Exercise and Control conditions in a counterbalanced order and served as their own controls.

Baseline evaluation

The Geriatric Depression Scale was used to assess participants' depression signs, while the 15-item Waterloo Handedness Questionnaire evaluated their hand preference. PD motor symptoms were assessed using the motor subsection of the Unified Parkinson's disease Rating Scale. Participants' general cognitive status was examined using the Montreal Cognitive Assessment.

In order to assess participants' fitness levels, a submaximal graded exercise test was completed. In this test, participants started with a 2 minute warm up with no load on the cycle ergometer. Participants began the graded exercise test cycling with a workload of 30 watts at 50 rotations per minute, then workload was increased every minute (15 watts/per increment unit) until participants achieved testing termination criteria. The protocol was terminated if two of the following criteria were achieved: participant's heart rate reached 70% of the age-predicted maximal heart rate (age-predicted max HR=208-(0.7* age)), respiratory exchange ratio was

greater than 1.1, participant rate of perceived exertion (RPE) was greater than 16 on a scale from 6 (no exertion) to 20 (maximal exertion) [16], or participant asked to stop. Gas exchange (levels of oxygen (O_2) and carbon dioxide (CO_2)) was recorded breath-by-breath using an Ergocard Cardiopulmonary Stress Test Metabolic Cart (Roxon medi-tech ltd. St-Leonard, Quebec, Canada). Heart rate was recorded at rest, continuously during, and after the test using a Polar HR monitor (Lachine, Quebec, Canada). VO_2 values at test termination were recorded and used as a reference of participants' fitness level. The influence of baseline fitness level on cognitive outcomes was examined as a confounding factor.

Demographic, clinical, and fitness level information at baseline are presented in Table 1.

Insert Table 1 here

Exercise condition

Immediately following the pre-tests of simple and choice RT, participants exercised on a recumbent cycle ergometer (700 Excite + Recline, Technogym USA©, Seattle, Washington) for 20 minutes at a set intensity of 50% heart rate reserve (HRR). Intensity prescription was defined based on the Karvonen method which was expressed in the equation Target HR = ([(HRmax - HRrest)* 0.5)]+HRrest) . Heart rate, workload, and rate of perceived exertion recordings from baseline graded exercise test were used as guidance to lead participants to the desired exercise intensity. Subsequently, participants rested for 15 minutes. After the resting period, they were invited to repeat the simple and choice RT tasks. The 15-minute delay period was chosen based on a meta-analysis by Chang and colleagues [17], which showed that time of test administration

following exercise significantly influenced studies' effect sizes. Specifically, it was found that assessments completed within 0–10 minute delay resulted in negative effects, whereas the largest positive effects were identified after 11–20 minute delay and smaller positive effects after 20-minute delay. Thus, a 15-minute delay was employed in this study as an intermediate value between minimum (11 minutes) and maximum (20 minutes) delays shown to reveal the largest positive effects on cognition after exercise. Exercise duration and intensity were also chosen based on this meta-analysis, where the largest effects of acute aerobic exercise on cognition were found after 20 minutes-long sessions of moderate intensity exercise (45% - 55% HRR; RPE 12-13).

Control condition

In the Control condition participants started with the simple and choice RT tasks and after the completion of these tests they were invited to sit on the same cycle ergometer in which the Exercise condition was performed for 20 minutes in the company of a trained volunteer. Later, participants sat on a chair for 15 minutes which corresponded to the resting period during the exercise session. Participants repeated both simple and choice RT tasks after the 15-minute delay.

Reaction Time tasks

Simple (SRT) and Complex Choice (CCRT) reaction time tasks from the *Feature Integration Test* [13] were used to assess the effects of exercise on energization, task-setting, and monitoring. The stimulus in these tasks was one of the four shapes: square, circle, triangle, or cross. The shapes were grey or coloured on a black background. For both tasks, stimuli were randomly presented at interstimulus intervals (ISI) varying between 3 s and 7 s. Each stimulus

stayed on the screen for 2 seconds or until a response was made. Each task was programed using MEL2 (Psychology Software Tools, Inc.), and responses were made on a Serial Response Box (Psychology Software Tools, Inc.) with five buttons (numbered 1-5 from left to right) aligned horizontally.

In the SRT, the stimulus was a grey square presented 50 times after 5 practice trials. Participants were instructed to press button number 1 in the serial response box as fast as possible whenever they saw the square. In the CCRT task, all shapes (square, circle, triangle, and cross) were presented in random order 102 times (one shape at a time), preceded by 10 practice trials. Each shape was coloured (red, blue, green, or yellow) and filled with a different pattern of internal lines (vertical, horizontal, diagonals to the right, or diagonals to the left). Thus, each stimulus varied in a combination of shape, colour and internal line orientation. A pre-determined target stimulus was defined by a specific combination of these three features (shape, colour, internal lines), while the other combinations were non-targets. The target stimulus occurred randomly on 25% of the trials. Participants were asked to respond to the target stimulus by pressing button number 1 with their right index finger, while they were asked to respond to non-target stimuli by pressing button 2 with their right middle finger on the serial response box. Four stimulus types existed in the CCRT task depending on the number of features shared with the target (0, 1, 2, or 3; where 3 was the actual target).

The acute effects of exercise on energization were assessed through the outcome measures overall RT. Since energization deficits are characterized by slowness in RT, positive effects of exercise on energization would be characterized by faster RT. The acute effects of exercise on task-setting were assessed through the outcome measures RT by stimulus type (target vs non-target) and number of false positive errors. Since deficits in task-setting are characterized

by an inability to establish the criteria defining a target stimulus in order to promptly and accurately select the correct response, then improvements in task-setting would be characterized by faster RT for target stimulus and decrease in false positive errors. The acute effects of exercise on monitoring were assessed through the outcome measures RT by ISI and total number of errors. Given that monitoring deficits lead to inability to anticipate/predict time of stimulus onset and to note an error for appropriate adjustment of behaviour, then positive effects of exercise on monitoring would be characterized by faster RT for long ISI compared to short as well as decrease in the total number of errors.

Statistical analysis

Repeated measures analysis of variance (RM ANOVA) was used to test differences in RT and RT coefficient of variation before and after Exercise and Control conditions (2 conditions (Exercise and Control) x 2 times (pre and post)). RM ANOVA was used to test differences in RT between experimental conditions for short and long ISI exclusively for SRT (2 conditions (Exercise and Control) x 2 time (pre and post) x ISI (short and long). RT at short ISI was calculated based on the mean RT for 3 and 4 seconds ISIs, while RT at long ISI was calculated based on the mean RT for 6 and 7 seconds ISIs. In addition, RM ANOVA was used to compare RT between conditions for stimulus type (2 conditions (Exercise and Control) x 2 time (pre and post) x 4 stimulus type (F0, F1, F2, target)) exclusively for CCRT. RM ANOVA was used to compare the total number of errors and error type for CCRT (2 conditions (Exercise vs Control) x 2 time (pre vs post) x 2 error types (false positive vs false negative)). Tukey post-hoc was used to examine significant differences and alpha level was kept at $p<0.05$. Finally, Pearson correlations were used to test whether changes in RT and accuracy were associated with participants' VO_2 value at test termination.

Results

Reaction time

The pre and post comparison of overall RT in each experimental condition revealed no differences in SRT following the Exercise or the Control session (Figure 1 - top). For CCRT, a main effect of assessment time ($F(1,19)=7.64$; $p=0.012$; $\eta_p^2=0.28$) showed that participants had faster RT at post- compared to pre-test regardless of experimental condition (Figure 1 - bottom) (Pre M=638.04, 95% CI [605.07,671.01]; Post M=619.13, 95% CI [584.40,653.87]).

Insert Figure 1 here

RT variability did not change from pre to post in all experimental conditions for SRT and CCRT (see Supplementary Material).

The analysis of RT for short and long inter-stimulus intervals aimed to demonstrate whether exercise could improve the ability of participants to predict stimulus occurrence. This is characterized by a decrease in RT for long ISI compared to short ISI. Following the same procedures as previous research, this analysis was run for the SRT but not CCRT [13]. A main effect of ISI demonstrated that, overall, participants showed the expected reduction in RT for longer ISI compared to shorter ($F(1,19)=96.86$; $p<0.001$; $\eta_p^2=0.83$) (Short ISI M=325.51, 95% CI [302.28,348.75]; Long ISI M=293.82, 95% CI [273.62,314.02]) (Figure 2). Importantly, these

findings occurred across experimental conditions, revealing no specific effect of exercise in participants' ability to predict stimulus occurrence. An interaction between assessment time and ISI was nearly significant ($F(1,19)= 4.13$; $p=0.056$; $\eta_p^2 =0.17$) .

Insert Figure 2 here

Finally, RT was analyzed with respect to stimulus type for the CCRT task. A main effect of number of features was found ($F(3,57)=96.67$ $p<0.001$; $\eta_p^2 =0.83$), showing that across experimental conditions participants had faster RT for stimulus sharing none or one feature with the target compared to stimulus sharing two features with the target or the target itself ($p<0.0001$) (F0: M=563.78, 95% CI [532.00,595.56]; F1: M=583.36, 95% CI [551.46,615.26]; F2: M=659.23, 95% CI [627.68,690.77]; target: M=680.04, 95% CI [637.01,723.06]) (Figure 3). There was no selective effect of exercise on response to target and non-target stimuli or any effect of assessment time.

Insert Figure 3 here

Accuracy

An interaction between experimental condition and assessment time approached significance ($F(1,19)=4.23$; $p=0.053$; $\eta_p^2 =0.18$) for the error measures (Figure 4) (EX Pre

M=0.95, 95% CI [0.45, 1.44]; EX Post M=1.22, 95% CI [0.75, 1.69]; CON Pre M=1.37, 95% CI [0.87,1.87]; CON Post M=1.05, 95% CI [0.66,1.43]).

Association between cognitive outcomes and fitness level

There were no associations between RT or accuracy and VO_2 values at test termination.

Discussion

In this study the effects of a single bout of exercise on cognition of individuals with PD was examined using RT tasks with varying complexity levels. These tasks have been previously used to evaluate the effects of localized frontal lobe lesions on cognitive processes underlying EF. Most importantly, the frontal areas found to be critical to each cognitive process are known to be anatomically and functionally linked to the basal ganglia through the basal ganglia-thalamo-cortical loops [13]. Given that previous studies with healthy young and older adults have found that a single bout of exercise leads to improvements in RT outcomes (i.e. faster RT) which were associated with increased brain activity in frontal brain areas [10, 11], it was predicted that individuals with PD would show improvements in performance (i.e. faster RT) in the tasks used in the current study after exercise. Contrary to this hypothesis, there were no selective effects of exercise on performance.

While no changes in RT were found in the simple RT task, faster RT was observed for the choice RT task in both Exercise and Control conditions. This latter result suggests that rather than a selective effect of exercise on cognition, participants were likely showing practice effects. These findings may have important implications to the interpretation of results from Ridgel et al. (2011), given that their study design lacked a Control condition and limited their ability to account for practice effects. The Control condition in the current study allowed us to demonstrate

that improvements in performance resulted from practice effects. Although these findings were not predicted, the absence of changes in behavioural measures following an acute bout of exercise has been previously reported in healthy individuals using different tasks [18]. Thus, one could suggest that task choice may have influenced the outcomes in the present study.

The tasks used in this study were carefully selected based on lesion studies that repeatedly showed the effects of localized frontal lobe lesions to each cognitive process. A recent meta-analysis has showed that the effects of an acute bout of exercise on cognition are small, but that this effect may increase depending on task complexity [17]. Thus, in the current study we had two tasks that were similar in structure, but that varied in complexity. Two tasks commonly used in previous investigations were modified versions of the Flanker Task [12] and the Stroop Test [11]. A commonality between these tasks is their large reliance on inhibitory control for successful performance. The tasks used in the current study were not designed to assess individuals' ability to inhibit pre-potent responses, therefore, it is possible that the effects of exercise on cognitive processes involved in EF are selective and may not have been captured by the tasks used in the present study. However, it is important to note that the effects of exercise on behavioural measures (null in this case) may not fully reflect the effects of exercise at neurophysiological level. Previous studies have reported changes in neurophysiological measures underlying cognition which were not detected in behavioural measures [12, 18]. Therefore, the effects of an acute bout of exercise on neurophysiological measures needs to be investigated in order to confirm whether or not individuals with PD are responsive to the effects of a single bout of exercise.

Alternatively, one could argue that individuals with PD were actually not responsive to a single bout of exercise. Previous studies have suggested that the effects of a single bout of

exercise on cognition may result from changes in circulating catecholamine (including dopamine), leading to increased arousal levels. While the depletion of dopaminergic activity is a hallmark of Parkinson's disease, there is growing evidence that levels of other catecholamines such as serotonin, noradrenaline and acetylcholine are also decreased in those with PD [19]. Thus, it could be argued that, from a neurotransmitter point of view, individuals with PD could have limited resources to acutely respond to the stress caused by exercise on brain activity. On the other hand, given that improvements in cognition have been found in individuals with PD in chronic exercise studies, it is possible that chronic exposure to exercise stimulation could lead to improvements in neurotransmitter activity. These improvements in neurotransmitter activity could result from increased activity of dopamine receptors [20] and neuroplastic effects driven by increased levels of neurotrophic factors [21]. Although highly speculative, this interpretation may help design future studies to investigate the acute effects of exercise on individuals with PD and potentially explain the underlying mechanisms of improvements found in chronic exercise studies in this population.

Limitations of this study include a small sample size considering the well-known inter-individual variability found in PD. Moreover, participants in this study had mild disease severity and relatively normal cognitive function. Therefore, the results of this study cannot be generalized to all individuals with PD. Although exercise intensity was set based on findings from a meta-analysis showing that larger effect sizes following moderate intensity exercise [17], evidence exists that high intensity exercise may be more beneficial than moderate exercise to elicit neurophysiological changes in the brain linked to improvements in cognition [22]. Finally, it is acknowledged that different theories exist regarding the role of frontal areas in cognitive

processing, thus results and interpretations from this study are focused on the investigation of one of these proposed models.

In conclusion, this study showed that an acute bout of exercise did not influence cognitive processes underlying EF in individuals with PD at the behavioural level. Future research should examine the effect of an acute bout of exercise on neurophysiological measures in order to confirm whether individuals with PD are responsive or not to the immediate effects of exercise on cognition. In addition, future studies using neuroimaging techniques should examine whether an acute bout of exercise can influence activation in the frontal lobes as well as basal ganglia areas in individuals with PD. Finally, in order to define the underlying mechanisms of the presence or absence of response to exercise stimulation, the assessment of neurotransmitter activity is a promising direction.

Conflict of Interest

None

Authors' contributions

Conceptualization and design of the study (CRAS, EAR, QJA); Acquisition of data (CRAS, QA); Analysis and interpretation of the data (CRAS, EAR, QJA), Drafting the article (CRAS); Article critical revision for important intellectual content (CRAS, EAR, QJA); Final approval of the submitted version (CRAS, EAR, QJA).

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References

[1] P. Barone, A. Antonini, C. Colosimo, R. Marconi, L. Morgante, T.P. Avarello, E. Bottacchi, A. Cannas, G. Ceravolo, R. Ceravolo, G. Cicarelli, R.M. Gaglio, R.M. Giglia, F. Iemolo, M. Manfredi, G. Meco, A. Nicoletti, M. Pederzoli, A. Petrone, A. Pisani, F.E. Pontieri, R. Quatrale, S. Ramat, R. Scala, G. Volpe, S. Zappulla, A.R. Bentivoglio, F. Stocchi, G. Trianni, P.D. Dotto, The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease, Mov. Disord. 24(11) (2009) 1641-9. doi: 10.1002/mds.22643

[2] A. Kudlicka, L. Clare, J.V. Hindle, Executive functions in Parkinson's disease: systematic review and meta-analysis, Mov. Disord.26(13) (2011) 2305-15. doi: 10.1002/mds.23868

[3] A.M. Owen, J. Doyon, A. Dagher, A. Sadikot, A.C. Evans, Abnormal basal ganglia outflow in Parkinson's disease identified with PET. Implications for higher cortical functions, Brain.121 (Pt 5) (1998) 949-65. doi: http://dx.doi.org/10.1093/brain/121.5.949

[4] R. Cools, R.A. Barker, B.J. Sahakian, T.W. Robbins, Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands, Cereb. Cortex 11(12) (2001) 1136-43. doi: 10.1093/cercor/11.12.1136

[5] C. Duchesne, O. Lungu, A. Nadeau, M.E. Robillard, A. Bore, F. Bobeuf, A.L. Lafontaine, F. Gheysen, L. Bherer, J. Doyon, Enhancing both motor and cognitive functioning in Parkinson's disease: Aerobic exercise as a rehabilitative intervention, Brain Cogn. 99 (2015) 68-77. doi: https://doi.org/10.1016/j.bandc.2015.07.005

[6] K. Tanaka, A.C. Quadros, Jr., R.F. Santos, F. Stella, L.T. Gobbi, S. Gobbi, Benefits of physical exercise on executive functions in older people with Parkinson's disease, Brain Cogn. 69(2) (2009) 435-41. doi: 10.1016/j.bandc.2008.09.008

[7] E.Y. Uc, K.C. Doerschug, V. Magnotta, J.D. Dawson, T.R. Thomsen, J.N. Kline, M. Rizzo, S.R. Newman, S. Mehta, T.J. Grabowski, J. Bruss, D.R. Blanchette, S.W. Anderson, M.W. Voss, A.F. Kramer, W.G. Darling, Phase I/II randomized trial of aerobic exercise in Parkinson disease in a community setting, Neurology 83(5) (2014) 413-25. doi: 10.1212/WNL.0000000000000644

[8] M.D. Sage, K.B. Beyer, M. Laylor, C. Liang, E.A. Roy, W.E. McIlroy, A single session of exercise as a modulator of short-term learning in healthy individuals, Neurosci. Lett. 629 (2016) 92-8. doi: https://doi.org/10.1016/j.neulet.2016.06.064

[9] A.L. Ridgel, C.H. Kim, E.J. Fickes, M.D. Muller, J.L. Alberts, Changes in executive function after acute bouts of passive cycling in Parkinson's disease, J. Aging Phys. Act.19(2) (2011) 87-98. doi: http://www.acutech.co.nz/Portals/Main/Acutech/MOTOmed/parkinson_gb_vt_ridgel_motomed_2.pdf

[10] K. Hyodo, I. Dan, K. Suwabe, Y. Kyutoku, Y. Yamada, M. Akahori, K. Byun, M. Kato, H. Soya, Acute moderate exercise enhances compensatory brain activation in older adults, Neurobiol. Aging 33(11) (2012) 2621-32. doi: 10.1016/j.neurobiolaging.2011.12.022

[11] H. Yanagisawa, I. Dan, D. Tsuzuki, M. Kato, M. Okamoto, Y. Kyutoku, H. Soya, Acute moderate exercise elicits increased dorsolateral prefrontal activation and improves cognitive performance with Stroop test, NeuroImage. 50(4) (2010) 1702-10. doi: 10.1016/j.neuroimage.2009.12.023

[12] K. Kamijo, Y. Hayashi, T. Sakai, T. Yahiro, K. Tanaka, Y. Nishihira, Acute effects of aerobic exercise on cognitive function in older adults, J. Gerontol. B Psychol. Sci. Soc. Sci. 64(3) (2009) 356-63. doi: 10.1093/geronb/gbp030

[13] D.T. Stuss, M.A. Binns, K.J. Murphy, M.P. Alexander, Dissociations within the anterior attentional system: effects of task complexity and irrelevant information on reaction time speed and accuracy, Neuropsychology. 16(4) (2002) 500-13. doi: http://dx.doi.org/10.1037/0894-4105.16.4.500

[14] D.T. Stuss, M.P. Alexander, Is there a dysexecutive syndrome?, Philos. Trans. of R. Soc. Lond. B Biol. Sci 362(1481) (2007) 901-15. doi: 10.1098/rstb.2007.2096

[15] F.A. Middleton, P.L. Strick, Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies, Brain Cogn. 42(2) (2000) 183-200. doi: 10.1006/brcg.1999.1099

[16] G. Borg, An Introduction to Borg's RPE-Scale, Mouvement, Ithaca, NY, 1985.

[17] Y.K. Chang, J.D. Labban, J.I. Gapin, J.L. Etnier, The effects of acute exercise on cognitive performance: a meta-analysis, Brain Res. 1453 (2012) 87-101. doi: 10.1016/j.brainres.2012.02.068

[18] K. Kamijo, Y. Nishihira, A. Hatta, T. Kaneda, T. Wasaka, T. Kida, K. Kuroiwa, Differential influences of exercise intensity on information processing in the central nervous system, Eur. J. Appl. Physiol. 92(3) (2004) 305-11. doi: 10.1007/s00421-004-1097-2

[19] A.A. Kehagia, R.A. Barker, T.W. Robbins, Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease, Lancet Neurol. 9(12) (2010) 1200-13. doi: 10.1016/S1474-4422(10)70212-X

[20] B.E. Fisher, Q. Li, A. Nacca, G.J. Salem, J. Song, J. Yip, J.S. Hui, M.W. Jakowec, G.M. Petzinger, Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early Parkinson's disease, Neuroreport. 24(10) (2013) 509-14. doi: 10.1097/WNR.0b013e328361dc13

[21] G. Frazzitta, R. Maestri, M.F. Ghilardi, G. Riboldazzi, M. Perini, G. Bertotti, N. Boveri, S. Buttini, F.L. Lombino, D. Uccellini, M. Turla, G. Pezzoli, C. Comi, Intensive rehabilitation increases BDNF serum levels in parkinsonian patients: a randomized study, Neurorehabil. Neural Repair 28(2) (2014) 163-8. doi: 10.1177/1545968313508474

[22] T. McMorris, A. Turner, B.J. Hale, J. Sproule, Beyond the Catecholamines Hypothesis for an Acute Exercise–Cognition Interaction: A Neurochemical Perspective, Exercise-Cognition Interaction, Elsevier (2016) 65-103. doi: https://doi.org/10.1016/B978-0-12-800778-5.00004-9

Table 1 Participants' demographic and clinical information

Participants	Age	Sex	Handedness	Education	MoCA	GDS	Disease duration	H&Y	UPDRS III	PD ON	Fitness level
PD (n=20)	66.55 (10.11)	13M/7F	19R/1L	16.05 (3.61)	27.1 (2.46)	7.35 (5.33)	7.75 (6.04)	I=4; II=14; III=2	16.35 (5.89)	121.78 (62.00)	17.92 (4.55)

Legend: MoCA – Montreal Cognitive Assessment; GDS – Geriatric Depression Scale; H&Y - Hohen & Yahr scale; Disease duration – years since diagnosis; UPDRS III– Unified Parkinson's disease Rating Scale motor subsection; PD ON – minutes since medication intake; Fitness level – peak oxygen uptake at test termination (VO2/kg). Values denote mean and standard deviation values, except for the H&Y scale which represents the number of cases per stage.

Figure 1 Participants showed no change in simple RT following both experimental conditions (top). Conversely, they showed faster RT in the choice RT following both Exercise and Control conditions (bottom).

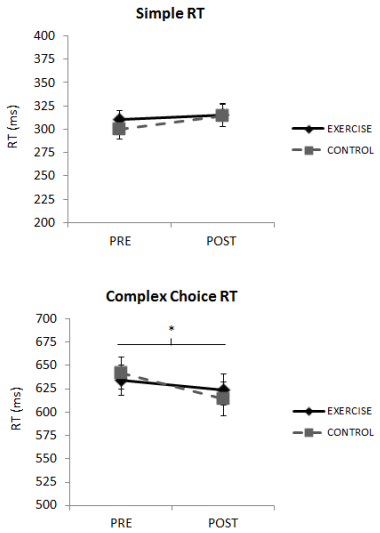

Figure 2 Participants showed faster RT for long ISI compared to short ISI regardless of experimental condition.

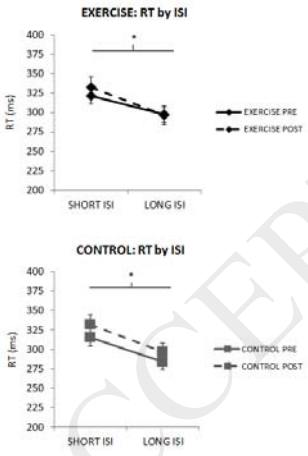

Figure 3 Participants responded faster to non-target stimuli sharing none or one feature with the target compared to stimuli sharing two features or the target itself, regardless of experimental condition or assessment time point.