41 - PHYSICAL EXERCISE'S EFFECT ON MEMORY-RELATED NEUROBIOLOGICAL IMPAIRMENTS OF ALZHEIMER'S DISEASE

JEFERSSON SILVA LUCINO[1]
NEMÉIA DE OLIVEIRA FARIAS[2]
SHIRLEY REGINA DE ALMEIDA BATISTA[3]
ARISTEIA NUNES SAMPAIO[4]
JAQUELINE DOS SANTOS VALENTE BARROS[5]

1. physical education student of Federal University of Acre, Rio Branco, Acre, Brazil;
2. Professora of Federal University of Acre, Rio Branco, Acre, Brazil;
3. Professora of Federal University of Acre, Rio Branco, Acre, Brazil
4. Professora of Federal University of Acre, Rio Branco, Acre, Brazil;
5. Professora of Federal University of Acre, Rio Branco, Acre, Brazil;

jefersson.lucino@sou.ufac.br

Doi: 10.16887/93.a1.41

Abstract

Introduction: The most prevalent symptom related to the Alzheimer's disease (AD) is the impairment in the Working Memory (WM), and the physical exercise display effectiveness, although, limited. **Objective:** To investigate the effect of physical exercise (PE) on working memory of older adults with memory impairment due to Alzheimer's disease. **Methods:** Forty- four subjects, all with Alzheimer's disease diagnose were divided into two groups (CG) that received only classical treatment, and Exercise Intervention Group (EIG) that received physical exercise plus classical treatment. The working memory was investigated before and after three months of intervention. The statistical procedure was conducted by Kruskal-Wallis with DUNN'S post hoc test, with a significance level of 5%. **Results:** The CG group display decrease in the WM, however, and EIG showed increasing in the WM performance. **Conclusion:** PE improves the WM of older adults with memory impairment due to Alzheimer's disease.
Key-words: Alzheimer's Disease; Classical Treatment; Physical Exercise Intervention. Older Adults.

Resumen

Introducción: El síntoma más prevalente relacionado con la enfermedad de Alzheimer (EA) es el deterioro de la Memoria de Trabajo (MT) y el ejercicio físico es efectivo, aunque limitado. Objetivo: Investigar el efecto del ejercicio físico (EF) en la memoria de trabajo de personas mayors con deterioro de la memoria por enfermedad de Alzheimer. Métodos: Cuarenta y cuatro individuos, todos diagnosticados con enfermedad de Alzheimer, fueron divididos en dos grupos (GC) que recibieron solo tratamiento clásico, y Grupo de Intervención con Ejercicio (GIE) que recibió ejercicio físico y tratamiento clásico. Se investigó la memoria de trabajo antes y después de tres meses de intervención. El procedimiento estadístico fue realizado por Kruskal-Wallis con la prueba post hoc de DUNN, con un nivel de significancia del 5%. Resultados: El grupo GC mostró una disminución en MT y el grupo GIE presentó un aumento en el desempeño de MT. Conclusión: El EF mejora la MT de personas mayores con deterioro de la memoria por enfermedad de Alzheimer.

Palabras clave: Enfermedad de Alzheimer, Tratamiento Clásico, Intervención de Ejercicio Físico, Adulto Mayor.

Résumé:
Introduction : Le symptôme le plus répandu lié à la maladie d'Alzheimer (MA) est l'altération de la Mémoire de Travail (MT) et l'exercice physique est efficace, bien que limité. But : Étudier l'effet de l'exercice physique (E.P.) sur la mémoire de travail des personnes âgées atteintes de troubles de la mémoire dus à la maladie d'Alzheimer. Méthodes : Quarante-quatre individus, tous diagnostiqués avec la maladie d'Alzheimer, ont été divisés en deux groupes (GC) qui n'ont reçu qu'un traitement classique, et un groupe d'intervention d'exercice (EIG) qui a reçu de l'exercice physique et un traitement classique. La mémoire de travail a été étudiée avant et après trois mois d'intervention. La procédure statistique a été menée par Kruskal-Wallis avec le test post hoc DUNN, avec un seuil de signification de 5 %. Résultats : Cependant, le groupe GC a montré une diminution de la TM et le groupe EIG a montré une augmentation de la performance de la TM. Conclusion : L'EP améliore la MT des personnes âgées présentant des troubles de la mémoire dus à la maladie d'Alzheimer.

MOTS-CLÉS : maladie d'Alzheimer, traitement classique, intervention d'exercice physique, personnes âgées.

Resumo

Introdução: O sintoma mais prevalente relacionado à doença de Alzheimer (DA) é o comprometimento da Memória de Trabalho (MT) e o exercício físico apresenta efetividade, embora limitada. **Objetivo:** Investigar o efeito do exercício físico (EF) na memória de trabalho de idosos com comprometimento da memória devido à doença de Alzheimer. **Métodos:** Quarenta e quatro *Fourty-four* indivíduos, todos com diagnóstico de doença de Alzheimer, foram divididos em dois grupos (GC) que receberam apenas tratamento clássico, e Grupo de Intervenção no Exercício (EIG) que recebeu exercício físico e tratamento clássico. A memória de trabalho foi investigada antes e após três meses de intervenção. O procedimento estatístico foi conduzido por Kruskal- Wallis com o teste post hoc do DUNN, com nível de significância de 5%. **Resultados:** No entanto, o grupo GC apresentou diminuição na MT e a EIG apresentaram aumento no desempenho da MT. **Conclusão:** O EF melhora a MT de idosos com comprometimento da memória devido à doença de Alzheimer.

Palavras Chave: Doença de Alzheimer, Tratamento Clássico, Intervenção por Exercício Físico, Idosos.

Introduction

The Alzheimer's Disease (AD) has an important prevalence among elderly, however, the cost to public health is very high and no perspective of cure are expected in the present day [1]. The AD shows a very high prevalence of degenerative and progressive dementia [2] is predicted to increase 4-fold by the year 2050 [3]. This disease decrease all mental functions with highlight to executive functions[4]. The neural deterioration tends to be associated with cognitive problems, among which, the most common is the learning, cognition, and memory [5].

The impairment of the working-memory (WM) is a classic effect among the various impairments associated with Alzheimer's Disease, however, a number of neurobiological effects

occur in relationship with cognitive deficits, including other notable sensory dysfunctions and consequent psychological disorders on the brain [6]. Typically, cognitive dysfunctions like working memory operability in the elderly population is the main behavioral symptom [7]. For instance, specific fall events are associated with low levels of working memory operability in the elderly population [7], which is an important issue, mainly due to the lack of a cure, since only palliative actions and drugs are mostly implemented, suggesting an urgency to alternatives.

The most effective, but, limited non-pharmacological intervention often is focused on physical exercises [8]. However, there is data suggesting that physical exercise is among a few effective activities of intervention for neurodegenerative diseases and other problems associated with cognition and memory, including on AD [9]. Therefore, the main objective is to investigate the effect of physical exercise (PE) on working memory of older adults with memory impairment due to Alzheimer's disease.

Materials and methods Volunteers and selection

From a group of 1096 older adults' patients who attended the Vila Vicentina Community Centre (CTIV), and Center for treatment of many mental diseases including the Alzheimer Disease, one of Assistance for Aged People localized in Belem of Pará, both in Brazil. Centre for Living with the Elderly (CCI), and the SESC located in the city of Porto Velho, and Vila Vicentina in Belem do Pará with various mental illnesses, including Alzheimer's and Parkinson's disease, only 88 older adult patients met all inclusion and exclusion criteria for eligibility to participate in this research. However, only *Fourty-four* displayed WM impairment. The diagnostic of dementia was performed several weeks by a multidisciplinary team composed by a General Practitioner, Psychiatrist, Psychologist, and Nurse involved in all living centers of recruitment following the National Institute of Neurological Communicative parameters Disorders (NINCDS) until the closing of the diagnostics. Regarding the present study, the Mini Mental State Examination (MMSE) was used for an objective measurement before and after the intervention program.

Procedures for inclusion and exclusion

Nurses trained to care for people with mental illness and other types of deteriorative diseases referred the elderly patients to the study. The diagnosis for AD followed the NINCDS. This diagnosis was performed by a medical or public service from the Unit of Health System from Brazil. In addition, questionnaires previously used corroborated the identification of these elderly patients, highlighting their dementia symptoms characteristics.

For inclusion in this study of Alzheimer's patients, the volunteers were required to score between 9 and 10 points on the Edmonton Frail Scale (EFS). In addition, all study participants were aged 65 to 80 years old, had an MMSE score of 11 or above, had basic participation in physical activity programs, and received medical authorization to participate in exercises at the level of the scheduled interventions.

Volunteers were not eligible if they had a disease or neurological disease syndrome that could be methodologically accepted for a clinical diagnosis of depression or a severe sensory deficit. Patients who had physical limitations that made them unable to perform a study task, those unable to recognize the content of the tasks of this study, who did not understand their participation in the research, and those who did not agree to sign the consent form to participate, were considered ineligible.

After completing the selection procedure, 88 seniors, all with Alzheimer's disease[10],

however, only 33 composed the final sample, because, only they showed WM impairment. The selection were randomly performed, and divided into two groups (n=22 each one). The subjects were divided into two groups (CG) that received only classical treatment, Exercise Intervention Group (EIG) that received the classical treatment plus physical exercise intervention. The working memory was investigated before and after three months of intervention.

Sample demographic characteristics

Group's demographic profiles were defined in terms of the following variables: (1) initial mental state (MMSE), (2) sex, (3) age, (4) income, (5) social income, (6) marital status, (7) education and (8) time of medication use due to illness. Overall, there was a similar distribution among the three groups for almost the entire demographic profile. Thus, due to the lack of apparent discrepancy between most of these variables, the statistical verification of the normality of the distributions was performed only between age and initial mental state, the only variables that presented apparent differences between groups. For this verification, the Student t test was applied in reference to $p <$ or $= 0.05$. Table 1 shows the descriptive characteristics of the study participants, with mean scores for all measures, including age, MMSE, and the comparisons between groups.

Variable	EIG (n=22)	CG (n=22)	*p* value
Age	70.59±4.83	70.46±4.47	EIG vs CG =.88
MMSE (pre-)	20.11±4.65	19.98±3.16	EIG vs CG =.20

Table 1. The volunteers of the GAE (n=22), GCP (n= 22), GCN (n= 22), and GCS (n=22) groups were submitted to the MMSE test as part of the inclusion and exclusion methodology. The results are described herein. The Student t test test was used with a significance of 5%.

Working Memory assessment

The Digit Span Test (DST) consists of checking short-term memory through working memory operations verification. This test concerns the functional aspect of memory related to an individual's ability to repeat, in the proper order, a sequence of items that may be letters, numbers, or words to evaluate the person's memory space. The test is characterized by a sequence of numbers and/or words to be remembered, and the sequence length is increased after each correct answer. The DST is reliable in its application, is high in its validity, and has been cross-validated [11], indicating that it is one of the most applicable tests for the examination of working memory functions.

Physical exercise protocols (PE)

The total program consisted of 40 minutes per session, 5 minutes for the warm-up, 30 minutes for the physical and mental training, and 5 minutes for the cool-down part, making a total of 40 minutes of physical exercise. The participants started from a seated position, and then they had to move to different standing positions and vice versa. The central part of the PE, which was practiced after the warm-up section, contained exercises for strength and resistance of the lower limbs, abdomen, upper limbs, balance, and overall motor coordination; all exercises were performed in a fun way, in circuits, and with the level of intensity determined by one's ability and perceived expended effort. To such a degree, when any of the subjects got tired or began feeling uncomfortable, they could pause and rest. Although the exercise was conducted in a self-

moderated way, all effort stimuli were directed to exhaustion. When the person needed to rest, we considered that the exercise reached the highest intensity level, which allowed us to suppose that the exercise program was progressive and had high-intensity characteristics.

All physical exercises included mental task practices that, when answered correctly, would give the participant a “license” to initiate the following physical exercise. In addition, coaches created situations that forced the participants to make quick decisions (such as high-speed side-to-side direction choices during moderate running) using their capacity of inhibitory control and mental processes linked to decision making. Finally, the cool-down section demanded the practice of breathing exercises and mind internalization, like exercises proposed by Eastern techniques such as Tai Chi Tchuen or yoga. The intensity of the resistance training was up to 60%, and the muscular strength was determinate by maximum repetition protocol as postulated by the ACSM [12], followed by a simple percentage calculation.

In summary, for load testing, all exercises selected were performed with a standard intensity until concentric failure. Then, a new load was implemented until subjects reached the concentric failure at 20 repetitions. Subsequently, the exercise was set up at 12 repetitions. The intensity was recalculated each one month. The equation was:

20 repetition reached with a standard load * % of work= nº of repetitions

Equation 1: equation for the calculi of the exercise intensity

Study type and research ethics

The present study was of an experimental type and was submitted to ethical evaluation by the Platform Brazil, as determined by the resolution of the National Health Council CNS 466/12 for approval under CAAE No. 67198217.0.0000.5524. After, approval number 2066823 was issued. In compliance with the ethical precept analogue to the same law, after all, doubts arising concerning the research were resolved, all volunteers and their legal representative signed a free Informed Consent Form before participating as a volunteer in this research.

Statistical Procedures

The statistical analysis followed three distinct phases. First, we used the Kolmogorov- Smirnov test (with Dallal-Wilkinson-Lille values for *p*) to determine data normality, which turned out to be parametric (p>0.05). The data were descriptively plotted based on the mean and standard deviation of the scores. Secondly, after determining the normality of the data distribution, the Kruskal-Wallis with DUNN’S post hoc test, with a significance level of 5%, was used to identify possible differences within and between groups using the scores the elderly individuals obtained at the pre-and post-intervention phases. Finally, the effect size of each type of intervention was calculated by Cohen’s ʃ test to three or more interactions, and to two interactions, the Cohen’s d test was used. For this test, a calculated difference between one set of scores compared to another (ʃ ²) between 0.02 and 0.14 was characterized as a small effect; and ʃ² between 0.15 and 0.34 was characterized as a medium effect, and an ʃ² with a value > 0.35 was considered a large effect. To Cohen’s d results between 0.20 and 0.39 is small, between 0.40 and 0.79 medium, and 0.80 or more large effect.

Results

The group displayed a homogenous distribution of age, marital status, and formal instruction.

There was a predominance of patients in the age range between 65 and 70 years old (30; 50.0%), followed by the age range from 71 to 75 years old (22; 36.6%) and 76 years or older (8; 13.3%). Concerning marital status, more than half of the participants were married (41; 67.83%), followed by those who were divorced (10; 16.6%) or widowed (9; 15.0%). The other demographic variables also show a similar distribution among the groups.

The combination of PE with classical treatment enhanced working memory

Regarding the working memory, the intragroup comparison related to GC presented 20.15±1.73 points in the baseline and 17.47+1.78 points after the intervention period which is a important decreased performance in WM (p>0.05). The EIG 19.85±4.74 points and 24.35±2.47 points, respectively, with improvement in performance (p> 0.05). Regarding intergroup comparison, the EIG-post presented differences for all CG (p<0.05). The size effect of EIG was moderate (r^2=0.63).

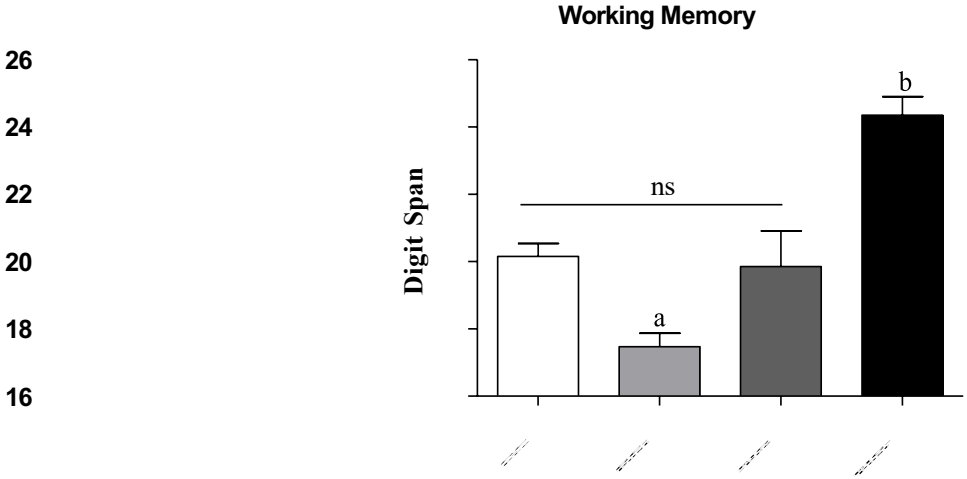

Figure 1: Mental parameters. Individuals diagnosed with Alzheimer's disease were separated into two groups (n= 22) control group (CG) that received only classical treatment, Exercise Intervention Group (EIG) that received the classical treatment plus physical exercise intervention. The working memory was investigated before and after three months of physical exercise intervention. All groups had their scores evaluated for working memory (Fig. 1A). The Kruskal Wallis test followed by the DUNN'S post hoc test was performed with 5% of significance. Figure 1 a= p<0.05 vs GC-Pre, b= p <0.0001 to all another comparison points.

Discussion

This research effort focus was to investigate the combined effects of physical exercise working-memory of older adults with AD. We discovered that the combination of classical treatment plus PE improved WM, and that the individual kept sedentary even receiving classical treatment is under a risk of deterioration of the mental performance. Physical exercise often improves cognition (e.g., executive functions, working memory, learning) and induce structural and functional brain plasticity [13,14] which can be the main adaptations in response the physical exercise, and the combination with the classical treatment can build a background to the pharmacological action. Populational, observational, and intervention studies indicate that exercising can reduce the risk of neurodegenerative diseases like dementia [15], Parkinson's disease [16], and AD [17] as here seemed.

For WM, the EIG showed significant improvement within and between groups in the post-intervention test (Fig. 1). In the CG decreased performance were noted in WM. Considering that the EIG received exercise program, these results, in part, corroborate the evidence that

physical exercise can improve the WM of people with AD [8]. Despite this, other works showed previously that physical exercise can enhance the working memory [18,19] reinforcing our data.

Another fact is related to the type of exercise modality implemented. For instance, we have applied resistance exercises with low volume and high-intensity. This choice was made due to security concerns of our aged volunteers, corroborating with another studies that showed that the WM is very responsive to the exercise intensity [20–22]. So, high-intensity resistance training was already sufficient to produce significant gains in the post-intervention test for WM, highlighting the effects over the WM on EIG.

Considering the current lack of a cure or an effective prevention against the deleterious effects of AD, the results of this research lead us to consider the application of physical exercises, as an effective tool for effect counteraction of AD in the brain function. Although its effects in AD cases with advanced impairments are unknown, at least in earlier stages, as well as at the beginning of this disease, such application may be highly recommendable. The primary finding of this investigation revealed that the methodological intervention composed PE improved the working memory of older adults with early-stage AD.

In summary, regarding the effects of PE on WM, the intervention here proposed displays a very important attenuation in the progression of the main behavioral symptom of AD. These changes benefited the group that received PE in comparison with their self after 3 months of intervention, and, if compared with the group that received only pharmacological intervention, the results were more notable yet, with effects commensurate with their performance on the tests that assessed competency associated with the cognitive variable studied here. Thus, the superior performance of the GAI concerning the CG in the assessment of working memory function reflects the best intervention promoted by the combination of the PE and Medical pharmacological strategy.

However, limitations are identified. First, the pharmacological strategy did not was controlled; second, the intensity did not was daily controlled, and the use of other tests that evaluate a working memory can be useful as a memory check for the test used here, or that, in, could make our ensemble units more robust. Due to this, although robust, and in consonance with the most important literature, our results need to be interpreted with care.

What does this article add? First, without surprise, our data display that the conventional pharmacological treatment against the neurological impairment related to Alzheimer's disease have a very limited effect against the deterioration of the WM. Yet, is clear that the PE have a powerful additional effect to pharmacological therapy resulting in a counteraction of the most prevalent effect of AD, which, in fact, can be an indicative to a most large use of this technic on the fight counter the Alzheimer's disease.

Conflict of Interest Statement

All authors state that this work does not have a conflict of interest of any nature.

Authorship Contributions

All authors contributed equally to study design, writing, data treatment, and final text approval, with VFS and JRVS performing all data collection, additionally, the ES make a language review.

Acknowledgements

The authors would like to thank to all participants, to SESI, and to Convivence Older Center in Proto Velho, Rondônia, Brazil.

Funding

CAPES/FAPERO by the financial support grant term 062-2016 under process number 011.331.0025-00.62/2014.

References

1. Guarino, A. *et al.* Executive functions in Alzheimer disease: A systematic review. *Front. Aging Neurosci.* **10**, (2019).
2. Lee, J. *et al.* SIRT3 deregulation is linked to mitochondrial dysfunction in Alzheimer's disease. *Aging Cell* (2018) doi:10.1111/acel.12679.
3. Kumar, A. & Tsao, J. W. *Alzheimer Disease: REVUE*. *StatPearls* (2018).
4. Garcia-Alvarez, L., Gomar, J. J., Sousa, A., Garcia-Portilla, M. P. & Goldberg, T. E. Breadth and depth of working memory and executive function compromises in mild cognitive impairment and their relationships to frontal lobe morphometry and functional competence. *Alzheimer's Dement. Diagnosis, Assess. Dis. Monit.* (2019) doi:10.1016/j.dadm.2018.12.010.
5. Kochhann, R. & Wilson, M. A. Introduction: Special issue on neuropsychology of aging. *Psychol. Neurosci.* (2019) doi:10.1037/pne0000176.
6. Curcio, C.-L. *et al.* A Regression Tree for Identifying Risk Factors for Fear of Falling: The International Mobility in Aging Study (IMIAS). *Journals Gerontol. Ser. A* (2019) doi:10.1093/gerona/glz002.
7. Lilamand, M. & Raynaud-Simon, A. Prevalence and consequences of frailty. *Prat. en Nutr.* **14**, 13–14 (2018).
8. Okamura, H., Otani, M., Shimoyama, N. & Fujii, T. Combined Exercise and Cognitive Training System for Dementia Patients: A Randomized Controlled Trial. *Dement. Geriatr. Cogn. Disord.* (2018) doi:10.1159/000490613.
9. Du, Z. *et al.* Physical activity can improve cognition in patients with alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. *Clinical Interventions in Aging* at https://doi.org/10.2147/CIA.S169565 (2018).
10. Rolfson, D. B., Majumdar, S. R., Tsuyuki, R. T., Tahir, A. & Rockwood, K. Validity and reliability of the Edmonton Frail Scale [4]. *Age and Ageing* vol. 35 526–529 at https://doi.org/10.1055/s-0043-120342 (2006).
11. Wambach, D. *et al.* Digit Span. in *Encyclopedia of Clinical Neuropsychology* 844–849 (2011). doi:10.1007/978-0-387-79948-3_1288.
12. Communications, S. *et al.* American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med. Sci. Sports Exerc.* (2002) doi:10.1249/MSS.0b013e3181915670.
13. Sexton, C. E. *et al.* A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. *Neuroimage* (2016)

doi:10.1016/j.neuroimage.2015.09.071.

14. Müller, P., Duderstadt, Y., Lessmann, V. & Müller, N. G. Lactate and BDNF: Key Mediators of Exercise Induced Neuroplasticity? *J. Clin. Med.* (2020) doi:10.3390/jcm9041136.

15. van Santen, J. *et al.* Effects of Exergaming in People with Dementia: Results of a Systematic Literature Review. *J. Alzheimer's Dis.* **63**, 741–760 (2018).

16. Furtado da Silva, V. *et al.* Quality of Life, Cognitive Impairment, Treatment, and Physical Exercise in Patients with Parkinson's Disease: A Review. *J. Exerc. Physiol.* (2017).

17. Macpherson, H., Teo, W. P., Schneider, L. A. & Smith, A. E. A life-long approach to physical activity for brain health. *Front. Aging Neurosci.* (2017) doi:10.3389/fnagi.2017.00147.

18. Liu-Ambrose, T. *et al.* Resistance Training and Executive Functions: A 12-Month Randomised Controlled Trial. *Arch. Intern. Med.* **170**, 170–178 (2010).

19. Tsai, C. L., Pan, C. Y., Chen, F. C., Wang, C. H. & Chou, F. Y. Effects of acute aerobic exercise on a task-switching protocol and brain-derived neurotrophic factor concentrations in young adults with different levels of cardiorespiratory fitness. *Exp. Physiol.* (2016) doi:10.1113/EP085682.

20. de Greeff, J. W., Bosker, R. J., Oosterlaan, J., Visscher, C. & Hartman, E. Effects of physical activity on executive functions, attention and academic performance in preadolescent children: a meta-analysis. *Journal of Science and Medicine in Sport* at https://doi.org/10.1016/j.jsams.2017.09.595 (2018).

21. Souza, T. R. *et al.* Exercício progressivo de curtíssima duração possui potente efeito sobre a memória de trabalho, controle inibitório e motricidade fina de adultos jovens sedentários. / Progressive exercise of very short duration has a potent effect on working memory, inhib. *Motricidade* **15**, 154–163 (2019).

22. Kelling, N. J. & Corso, G. M. The effect of spatial working memory capacity on ball flight perception. *J. Hum. Sport Exerc.* (2018) doi:10.14198/jhse.2018.134.04.