INFLUENCE OF ACUTE PHYSICAL EXERCISE ON COGNITIVE AND MOTOR BEHAVIOR IN AN EXPERIMENTAL MODEL OF ALZHEIMER'S DISEASE

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INFLUÊNCIA DO EXERCÍCIO FÍSICO AGUDO NO COMPORTAMENTO COGNITIVO E MOTOR EM MODELO EXPERIMENTAL DE ALZHEIMER

INFLUENCIA DEL EJERCICIO FÍSICO AGUDO EN EL COMPORTAMIENTO COGNITIVO Y MOTOR EN MODELO EXPERIMENTAL DE ALZHEIMER

Meiriélly Furmann[1] (Physiotherapist),
Denise Barth Rebesco[1] (Physical Education Professional),
Leandro Smouter[1] (Physical Education Professional),
Andressa Panegalli Hosni[2] (Physiotherapy Student),
Ivo Ilvan Kerppers[2] (Physiotherapist),
Aristides M. Machado-Rodrigues[3,4] (Physical Education Professional),
Luis Paulo Gomes Mascarenhas[5] (Physical Education Professional)

1. Universidade Estadual do Centro-Oeste, Interdisciplinary Community Development Graduate Degree Program, Irati, PR, Brazil.
2. Universidade Estadual do Centro-Oeste, Laboratório de Neuroanatomia e Neurofisiologia, Guarapuava, PR, Brazil.
3. Universidade de Coimbra, Coimbra, Portugal.
4. Escola Superior de Educação de Viseu, Instituto Politecnico de Viseu, Viseu, Portugal.
5. Universidade Estadual do Centro-Oeste, Interdisciplinary Community Development Graduate Degree Program, Department of Physical Education, Irati, PR, Brazil.

Correspondence
Luis Paulo Gomes Mascarenhas.
Universidade Estadual do Centro-Oeste, Rod. Pr (153. Km 7), Irati, PR, Brazil. 84500-000.
lmascarenhas@unicentro.br

ABSTRACT

Introduction: Aging causes alterations in various executive and cognitive functions, mainly related to the incidence of dementia, especially Alzheimer's disease (AD). Several studies mention physical exercise as a preventive resource for depressive symptoms. Objective: To investigate the cognitive and behavioral alterations related to AD that are capable of slowing disease progression and its complications. Methods: The sample consisted of 10 male Wistar rats, divided into 2 groups (n = 5), swimming and Alzheimer + swimming, with a 6-day intervention protocol. The elevated plus maze test was used to assess anxiety, the Morris water maze for spatial memory, the isolation box for aversive memory, and the open field test to assay motor behavior. Results: There was improvement in spatial memory in the Swimming group (169 ± 142.9 x 24.2 ± 31.3), but motor behavior deteriorated after exercise. An increase in anxious behavior (8 ± 13.03 x 67.8 ± 48.1) was observed in the animals with AD. This is a relevant characteristic of the disease, which did not improve after acute exercise. By analyzing the size effect, it was possible to observe a difference in the Alzheimer + swimming group in terms of reduced anxiety and improved motor behavior after exercise. Despite the benefits of physical exercise for AD symptoms, there is still no consensus on the type of physical exercise and length of intervention necessary to achieve a positive response as a treatment method, since studies are yet to confirm this fact in an acute or chronic manner. Conclusion: Acute physical exercise was not fully effective as a means of treating behavioral alterations related to AD, but had a mean effect on the size effect analysis of motor behavior and anxiety, specifically. ***Level of evidence IV; Investigation of treatment outcomes.***

Keywords: Alzheimer Disease; Exercise; Aging; Memory; Motor behavior.

RESUMO

Introdução: O envelhecimento causa alterações de diversas funções executivas e cognitivas, principalmente relacionadas à incidência de demências, em especial, a doença Alzheimer (DA). Diversos estudos mencionam o exercício físico como um recurso preventivo de sintomas de depressão. Objetivo: Investigar as alterações cognitivas e comportamentais relacionadas à DA capazes de retardar a progressão da doença e suas complicações. Métodos: A amostra foi composta por 10 ratos Wistar machos divididos em 2 grupos (n = 5), Natação e Alzheimer+Natação, com protocolo de 6 dias de intervenção. Foram realizadas avaliações da ansiedade pelo teste de labirinto elevado em cruz, memória espacial pelo labirinto aquático de Morris, memória aversiva pelo teste de aversão em caixa de isolamento e comportamento motor por meio do teste Open Field. Resultados: No grupo Natação houve melhora na memória espacial (169 ± 142,9 x 24,2 ± 31,3), porém verificou-se comportamento motor pior depois do exercício. Igualmente, observou-se aumento do comportamento de ansiedade (8 ± 13,03 x 67,8 ± 48,1) nos animais com DA, característica relevante da doença, que não apresentou melhora após o exercício agudo. Através da análise do Size effect foi possível observar que houve diferença no grupo Alzheimer+Natação na diminuição da ansiedade e melhora do comportamento motor após o exercício. Apesar dos benefícios do exercício físico para os sintomas da DA, ainda não existe um consenso sobre o tipo de exercício e o tempo de intervenção necessários para que se tenha uma resposta positiva como método de tratamento, uma vez que ainda não existem estudos que comprovem esse fato de maneira aguda ou crônica. Conclusão: O exercício físico de forma aguda não se mostrou totalmente eficaz como tratamento das alterações comportamentais com relação à DA, porém obteve um efeito médio na análise pelo Size effect sobre o comportamento motor e a ansiedade, especificamente. ***Nível de evidência IV; Investigação dos resultados do tratamento.***

Descritores: Doença de Alzheimer; Atividade física; Envelhecimento; Memória; Comportamento motor.

RESUMEN

Introducción: El envejecimiento causa cambios de diversas funciones ejecutivas y cognitivas, relacionadas con la incidencia de demencias, en especial, la enfermedad de Alzheimer (EA). Diversos estudios mencionan el ejercicio

físico como *un recurso preventivo de síntomas de depresión. Objetivo: Investigar las alteraciones cognitivas y de comportamiento relacionadas a la EA capaces de retardar la progresión de la enfermedad y sus complicaciones. Métodos: Diez ratas Wistar machos divididas en 2 grupos (n = 5), Natación y Alzheimer+natación, con protocolo de intervención de 6 días. Se realizaron evaluaciones de la ansiedad por la prueba del laberinto elevado en cruz, memoria espacial por el laberinto acuático de Morris, memoria aversiva por la prueba de aversión en caja de aislamiento y comportamiento motor por de la prueba de campo abierto. Resultados: En el grupo Natación hubo mejoría en la memoria espacial (169 ± 142,9 x 24,2 ± 31,3), pero se observó comportamiento motor peor después del ejercicio. También se observó un aumento del comportamiento de ansiedad (8 ± 13,03 x 67,8 ± 48,1) en los animales con EA, característica relevante de la enfermedad, que no presentó mejoría después del ejercicio agudo. A través del análisis del Size effect fue posible observar que hubo diferencia en el grupo Alzheimer+Natación en la reducción de la ansiedad y de mejora del comportamiento motor después del ejercicio. A pesar de los beneficios del ejercicio* físico *en los síntomas de la EA, todavía no hay consenso sobre el tipo de ejercicio* físico y *el tiempo de intervención necesarios para tener una respuesta positiva como método de tratamiento, ya que aún no existen estudios que demuestren ese tipo de hecho agudo o crónico. Conclusión: El ejercicio* físico de forma aguda no *fue totalmente eficaz como tratamiento de las alteraciones de comportamiento con relación a la EA, pero obtuvo un efecto promedio en el análisis por el Size effect sobre el comportamiento motor y la ansiedad, específicamente.* ***Nivel de evidencia IV; Investigación de los resultados del tratamiento.***

Descriptores: *Enfermedad de Alzheimer; Actividad* física; *Envejecimiento; Memoria; Comportamiento motor.*

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INTRODUCTION

Cognitive aging speeds up the process of cerebral atrophy, involving dilation of sulci and ventricles, loss of neurons, presence of senile plaques and neurofibrillary tangles, deposition of beta-amyloid protein, and degeneration of granulovacuolar bodies,[1] mainly causing changes in functions, such as language, memory, judgment, temporospatial orientation, and executive function. One of the main factors related to the growth of this subset of the population is the increase in the incidence of dementias, especially Alzheimer's disease (AD).

Behavioral and cognitive changes occur with the progression of AD, requiring attention and care with medication use, necessitating institutionalization, and increasing the burden on caregivers and family members. In addition to neurophysiological and neurochemical changes that interfere with mood and cause depressive symptoms, they are widely involved in the increase in morbidity and mortality and, consequently, in the increased use of health care services.[2,3] Therefore, studies investigating cognitive and behavioral changes related to AD are necessary to better understand these changes and to propose new interventions, including alternative treatments to drugs and other already known treatments (e.g., donazepil or Eranz®) that are capable of slowing the progression of the disease and its complications.

According to Cotman and Bertchtold,[4] physical exercise can cause biochemical and physiological changes that improve brain performance and function, promoting greater protection against neurodegenerative diseases and enhancing brain performance and learning ability. According to Cooper,[5] regular physical exercise cumulatively decreases stress or tension owing to the increased production of endorphins, which act on the nervous system and reduce environmental stress, thereby preventing or reducing depressive disorders.

Several studies mention physical exercise as a preventive measure against depressive symptoms and motor alterations.[6,7] Thus, exercise is an important subject to explore as a method of treatment of AD. However, the acute effect of exercise on the complications of AD is still not conclusive, as those studies were performed in healthy individuals in whom exercise had a preventive character.

Accordingly, the present study aimed to analyze the influence of acute physical exercise on motor and cognitive behavior in an AD experimental model, based on the hypothesis that acute physical exercise can attenuate the symptoms of AD.

METHODS

This study was approved by the Ethics Committee for Animal Use of the State University of the Central West under opinion 025/2016. The sample consisted of 10 animals of the *Rattus norvegicus* breed, Wistar line, male, weighing between 200 and 250 g, and aged 2 months. The animals were randomly divided into two groups, as described in Table 1.

Experimental Surgery

The animals of the Alzheimer + Swimming group (n = 5) were anesthetized through intraperitoneal injection in the abdomen with a solution in the proportion of 80 mg/kg ketamine hydrochloride (ketamine, 10 mL vial) to 15 mg/kg xylazine hydrochloride (Dopaser®, 10 mL vial). The animals were then taken to an INSIGHT® stereotaxic apparatus, where their heads were fixed by the temporal bone and upper incisors. The coordinates used were as follows: anteroposterior = 0.0 mm, mediolateral = ±0.8 mm, and dorsoventral = 4.0 mm, with the bregma as the reference, and the lambdoid and bregmatic sutures being in the same horizontal plane. Beta-amyloid toxin$_{1-42}$ (3 μL) was injected using a 10-μL Hamilton syringe, with 0.02 μL being injected every minute, adding up to 9 min of induction. For analgesia, tramadol hydrochloride was used at a dose of 10 mg/kg every 12 h intraperitoneally for 7 days.[8]

After inducing senile plaque formation and neurofibrillation, the animals rested for 30 days to allow inflammatory and neurodegenerative processes of the hippocampal neurons to take place, as demonstrated in Figure 1, which shows images of the hippocampus region of the Alzheimer + Swimming group (A and B) and the Swimming group (C and D). In A and B, the black arrows indicate the arrangement of the senile plaques in the middle of the nerve cells. On the other hand, in C and D, the white arrows indicate the arrangement of several neuronal cells without the presence of senile plaques, as dementia was not induced in these animals. This confirms that the experimental protocol is efficient with respect to the induction of AD.

Table 1. Experimental groups.

Groups (n = 5)	Description	Intervention
Swimming	Group without induction of senile plaques	Swimming protocol
Alzheimer + Swimming	Group with induction of senile plaques	Swimming protocol

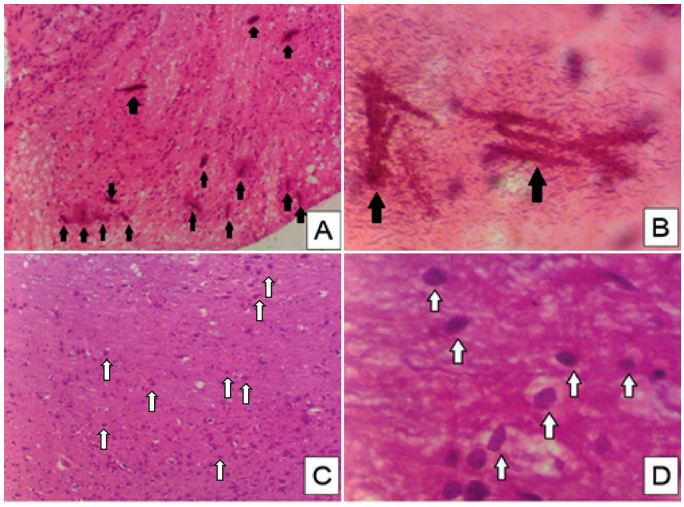

Figure 1. Histology of the rat hippocampus (A, B = presence of Alzheimer; C, D = absence of senile plaques).

Swimming Protocol

The animals (n = 10) underwent 30 min of daily training without intervals, for 6 consecutive days. Before the beginning of the intervention, the animals were given 3 days to adapt to the aquatic environment. A lead training weight was used, representing 5% of the animal's body mass.

Behavioral Tests

Anxiety

In the analysis of anxiety-related factors, the elevated plus-maze was used. The test takes 5 min, as the rats show more vigorous escape reactions in the first 5 min when they are placed in the arms of the maze. Behaviors such as freezing (the moment when the animal is immobile), grooming (the act of scratching/cleaning with the front paws), and longer time in the closed arms of the maze are related to a higher anxiety index.[9]

Spatial Memory

The Morris water maze test was applied to assess the animals' ability to acquire spatial memory by measuring the latency for the animal to find a submerged platform in a tank with opaque water.[10] In the training phase, the rats performed 5 daily trials, with a maximum time of 54 s for each trial and 30-s intervals to find the platform located at the center of the tank. For each test, the animal was placed facing the tank wall, departing from pseudo-random points.

Aversive Memory

Initially, the rats were trained in the fear conditioning task. Briefly, this task uses a training chamber (model MED-VFC2-SCT-R; Med Associates Inc., St. Albans, VT, USA), which consists of an aluminum box (35 × 35 × 35 cm) with a floor made of parallel stainless-steel bars spaced 0.8 mm apart. This training box is located inside a larger, acoustically isolated box to attenuate the interference of external sounds.

The mnemonic performance was measured and expressed in the time the rat remained in the freezing state. This behavior was assessed as an index of fear in rats.[11]

Motor Behavior

To evaluate motor activity, the open field test was used, in which the animals were carefully placed at the center of the open field and allowed to freely explore the field for 5 min. Three motor parameters were evaluated: number of quadrants (the number of times the animal moved from one quadrant to another with all four paws), rearing (the number of times the animal stood on the hind paws), amount of fecal matter, and time of immobility (time in seconds that the animal remained immobile).[12]

Euthanasia

The animals were anesthetized with 80 mg/kg ketamine and 15 mg/kg xylazine. After anesthesia induction, the animals received lethal doses of 20 mg/kg thiopental intraperitoneally.

Statistical Analysis

For data analysis, the Shapiro-Wilk test for normal distribution and Levene's test for homogeneity of variances were performed. In situations in which there was normality and homogeneity, the comparison of groups was performed through factorial analysis (factorial analysis of variance), with pairwise post hoc and Bonferroni correction. On the other hand, in situations in which there was neither normality nor homogeneity, the comparison of groups was performed through non-parametric analysis of Kruskal-Wallis H variance, with a mean-ranks post-hoc test. All tests adopted an error probability of <0.05 for inferring a significant difference. Effect size analysis was also performed using the Cohen test with 95% confidence intervals.

RESULTS

Table 2 shows the values related to the animals' anxiety. In the Alzheimer + Swimming group, there was a significant difference between pre- and post-induction, proving the presence of AD (p = 0.00) as the animals became more anxious (represented by the freezing variable), the main characteristic analyzed in this test. Moreover, there was a statistically significant difference between pre-induction and post-swimming, in which the animals spent more time in the closed arm, which shows a higher level of anxiety.

Table 3 shows the values related to the spatial memory of the animals. In the Swimming group, a significantly positive influence of acute exercise (p = 0.001) was observed. However, in the Alzheimer + Swimming group, no statistically significant difference was seen.

Table 4 shows the values related to aversive memory. None of the comparisons obtained a statistically significant difference.

Table 5 shows the variables related to the animals' motor behavior. A significant difference was obtained in the Swimming group, in which a decrease in motor performance was observed on the basis of the animals' displacement in the quadrants. This shows that, in this case, acute physical exercise was not beneficial; however, there was no increase in the characteristics of fear and anxiety, as shown by the Alzheimer + Swimming group by freezing (p = 0.001).

Table 6 shows the results of the effect size analysis for sample size, in which the data were compared among the evaluated groups. Despite the small sample size and although some analyses did not present a significant statistical difference, the effect size analysis revealed a relevant difference.

Table 2. Comparative analysis between the phases of the Swimming and Alzheimer + Swimming groups for the anxiety variables.

Anxiety	Swimming		Alzheimer + Swimming		
	Pre-swimming	Post-swimming	Pre-induction	Post-induction	Post-induction + swimming
Freezing (s)$^{\Omega}$	4.8 ± 3.96	3.4 ± 2.6	8 ± 13.03^{A}	67.8 ± 48.1	18 ± 18.2
Grooming (n)$^{\Omega}$	3.2 ± 1.09	2.6 ± 1.94	2.6 ± 1.51	3 ± 2.12	3.2 ± 2.28
OAT(s)$^{\Omega}$	34.4 ± 22.05	7.2 ± 5.8	14.6 ± 22.4	0 ± 0	4.0 ± 8.9
CAT (s)$^{¥}$	265.6 ± 22.05	292.8 ± 5.8	147.4 ± 112.3	233.2 ± 130.4	275 ± 11.18

A = difference between pre and post; ¥ = parametric (analysis of variance); Ω = non-parametric (Kruskal-Wallis) (p ≤ 0.05). OAT, open-arm time; CAT, closed-arm time.

Table 3. Comparative analysis between the phases of the Swimming and Alzheimer + Swimming groups for spatial memory.

Spatial memory	Swimming		Alzheimer + Swimming		
	Pre-swimming	Post-swimming	Pre-induction	Post-induction	Post-induction + swimming
Latency(ies)$^{\Omega}$	169 ± 142.9^{A}	24.2 ± 31.3	53.2 ± 54.2	6.6 ± 4.6	48.4 ± 71.2

A = difference between pre and post; Ω = non-parametric (Kruskal-Wallis) ($p \leq 0.05$).

Table 4. Comparative analysis between the phases of the Swimming and Alzheimer + Swimming groups for aversive memory.

Aversive Memory	Swimming		Alzheimer + Swimming		
	Pre-induction	Post-induction	Pre-induction	Post-induction	Post-induction + swimming
Freezing (s)$^{\Omega}$	9 ± 7.0	6.4 ± 4.9	7.4 ± 4.8	5.8 ± 5.4	6.8 ± 3.2

Ω = non-parametric (Kruskal-Wallis), ($p \leq 0.05$).

Table 5. Comparative analysis between the phases of the Swimming and Alzheimer + Swimming groups for the motor behavior variables

Motor behavior	Swimming		Alzheimer + Swimming		
	Pre-swimming	Post-swimming	Pre-induction	Post-induction	Post-induction + swimming
Rearing (n)¥	19 ± 7.7	5.4 ± 2.8	29.8 ± 13.8	19 ± 8.4	5.6 ± 5.3
Freezing (s) ¥	5.2 ± 4.6	7.0 ± 8.3	6.6 ± 9.3^{A}	92.4 ± 52.3	141 ± 33.9
Feces (n)$^{\Omega}$	4 ± 1.41	1.2 ± 0.44	5.6 ± 1.14	2.4 ± 1.51	3.6 ± 1.81
Latency at the center (s)$^{\Omega}$	1.2 ± 1.78	38.6 ± 41.5	11 ± 11.5	9.4 ± 3.5	4.2 ± 6.57
Q1 (n) ¥	5.4 ± 2.1^{A}	1.6 ± 1.14	7 ± 2.54^{A}	2.6 ± 2.07	1.4 ± 1.14
Q2 (n) ¥	6.4 ± 2.0^{A}	1 ± 1	5.4 ± 2.3^{A}	2.4 ± 2.3	1.4 ± 1.5
Q3 (n) ¥	5.2 ± 0.83^{A}	6 ± 0.89	5.6 ± 3.3	3.2 ± 2.38	2 ± 1.22
Q4 (n) ¥	5.4 ± 1.81^{A}	1.4 ± 0.89	5.6 ± 2.79	3.4 ± 2.3	2.4 ± 1.14

A = difference between pre and post; ¥ = parametric (analysis of variance); Ω = non-parametric (Kruskal-Wallis) ($p \leq 0.05$).

Table 6. Effect size analysis (*size effect*).

Effect size		Pre/post-swimming		Pre/post-induction		Pre-induction/pre-swimming	
		d	r	d	r	d	r
Anxiety	Freezing	0.34	0.17	-1.67	-0.64*	1.3	0.56ŧ
	Grooming	0.38	0.18	-0.21	-0.1*	-0.09	-0.04*
	OAT	1.68	0.64ŧ	0.92	0.41ŧ	-0.6	-0.3
	CAT	-1.68	-0.64*	-0.7	-0.33*	-0.4	-0.22*
Spatial memory	Latency	1.4	0.57ŧ	1.21	0.51ŧ	-0.82	-0.38*
Aversive memory	Freezing	0.43	0.21	0.31	0.15	-0.22	-0.11*
Motor behavior	Rearing	2.34	0.76ŧ	0.94	0.42ŧ	1.9	0.69ŧ
	Freezing	-0.26	-0.13*	-2.28	-0.75*	-1.1	-0.48*
	Feces	2.71	0.80Ŧ	2.43	0.77ŧ	-0.72	-0.34*
	Latency	-1.27	-0.53*	0.18	0.09	0.98	0.44ŧ
	Q1	2.26	0.74ŧ	1.92	0.69ŧ	0.73	0.34
	Q2	3.41	0.86Ŧ	0.86	0.39	1.03	0.45ŧ
	Q3	-0.92	-0.42*	0.83	0.38	0.63	0.3
	Q4	2.8	0.81Ŧ	0.86	0.39	0.55	0.26

d = mean difference; r = effect size; CI = 95% confidence interval; Ŧ = large effect (≥0.80); ŧ = medium effect (0.40–0.70); *negative values = no effect. OAT, open-arm time; CAT, closed-arm time.

DISCUSSION

The present study aimed to analyze the influence of acute physical exercise on motor and cognitive behavior in an AD experimental model. Spatial memory after acute physical exercise has been proven to be better in healthy individuals, as exercise has beneficial effects on brain plasticity and cognitive function owing to angiogenesis and increased cerebral blood flow, which consequently increase oxygenation and the transport of nutrients and neurotrophins.[13] This corroborates the findings of Erickson et al.,[14] who observed that high levels of aerobic physical exercise influence the preservation of hippocampal volume and promote better performance in spatial memory tests in elderly persons without dementia. In contrast to these known benefits, in this study, there was no improvement in the group of rats with AD, as spatial memory is impaired in these animals. Furthermore, this group presented lower latency values after the induction of AD, which may have occurred because of the influence of external environmental factors such as temperature, noise, or ambient light.[15] The study by Rogge et al.[16] demonstrated that 12 weeks of balance training in healthy adults had positive effects on spatial memory and cognition; however, it is still not clear what kind of exercise has better effects on cognition even in healthy individuals.

The practice of physical exercise has been described as an important factor for healthy aging because of its benefits to the central nervous system, as it promotes alteration of cerebral monoamines such as dopamine, serotonin, and noradrenaline, in addition to increasing blood perfusion, which improves oxygenation and consequently brain function. According to Cotman and Bertchtold,[4] physical exercise may increase the levels of brain-derived neurotrophic factor, in addition to other growth factors, thus stimulating neurogenesis, mobilizing the expression of genes that benefit the brain plasticity process, increasing the brain's resistance to damage, improving learning and mental performance, and promoting axonal regeneration of neurons in healthy individuals.

Although it remains a controversial issue, a systematic review by Coelho et al.[17] reported that regular systematic physical activity, preferably the kind associated with cognitive stimulation, is beneficial either as a preventive measure against AD or for the temporary improvement of cognitive functions, particularly attention, executive functions, and language in patients with AD. However, there is still no consensus on the appropriate type of physical exercise and the duration of intervention, and positive results have not been achieved for all symptoms and characteristics of the disease.

Although it did not show a statistically significant difference in relation to anxiety, which was elevated after the induction of AD (represented by increased freezing time), acute physical exercise had a medium effect in the Alzheimer + Swimming group in the Cohen test.[18] In the study by Barbosa and de Lima,[19] in which a greater number of animals were included and the same methodology was used, a significant decrease in anxiety was observed. Although they did not present a statistically significant difference, the factors of shorter open-arm time and longer closed-arm time seem to be related to the defensive response; that is, between the avoidance-exploration conflict in relation to the open arm.[20]

Meanwhile, aversive memory presented no difference. This finding corroborates that of Hopkins et al.[21] and Radak et al.,[22] who evaluated exercise-induced memory by using object recognition tests and did not observe inhibitory avoidance/aversive memory even at 2 and 8 weeks after training. In these studies, the training time was probably insufficient to cause any positive changes in the animals' aversive memory.

Finally, motor behavior analysis demonstrated that AD impairs the animals' performance and displacement, possibly because of neuronal death and synaptic degeneration, as described by Machado et al.[23] Acute physical exercise in this case led to a decrease in motor activity, although values related to anxiety and fear did not increase. As the mechanism used by the active beta-amyloid peptide alters the motor behavior of animals, the animals remain in a state of stagnation, such as a depressive state.[24] In the effect size analysis, an improvement in the animals'

exploratory motor behavior was observed after acute physical exercise in the group with AD, as well as a decrease in the latency, characterized by the animals' permanence at the center of the platform, both with a medium effect. This demonstrates the anxiolytic effect of aerobic physical exercise, as reported by Gomes et al.[25]

The present study is extremely important because the aging of the population increases the risks of neurological diseases, which, in turn, require innovative methods of treatment that can improve the quality of life of this population. Some limitations of the present study should be considered, mainly the small sample size, which might have caused large discrepancies in the statistical analysis results, even with the analysis of effect size.

CONCLUSION

Acute physical exercise in healthy animals was efficient in improving and preventing behavioral and cognitive alterations in relation to spatial memory.

Although acute exercise did not present significant differences, the effect size analysis demonstrated that acute exercise, in terms of motor behavior variables, is efficient as a form of treatment for AD.

Future studies with larger samples and different analyses should be performed to confirm the results of this study.

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