Original Research Article

HIIT IMPACTS THE BDNF AND PHOSPHORILATED TAU IN ALZHIMER'S DISEASE CORRELATED WITH BLOOD LACTATE: A RANDOMIZED CONTROL TRIAL

Abstract

Aims: This study examines the effects of high-intensity body weight interval training (PMED) on brain-derived neurotrophic factor (BDNF) and phosphorylated-TAU protein (p-TAU) in Alzheimer's disease (AD) and their relation to blood lactate concentration.

Study design: An experimental randomized control trial was conducted.

Place and Duration of Study: The study took place at Vila Vicentina Community Center, the Elderly Support Center of the University of Pará (UEPA), the Senior Living Center (CCI), and SESC Porto Velho, Brazil, between 2016 and 2018.

Methodology: Seventy-eight seniors diagnosed with AD were divided into three groups: HIIT, MICT, and a sedentary control group. The HIIT group engaged in 30 minutes of exercise at 80-90% of maximal heart rate, while the MICT group walked for 30 minutes at 60% of maximal heart rate. Both exercise groups performed their respective activities three times per week for three months, composing 36 exercise sessions. Pre- and post-intervention measurements of BDNF and p-TAU were conducted and the lactate correlation were done.

Results: The HIIT group showed a significant increase in BDNF and a decrease in p-TAU concentrations ($p<0.0001$), with a stronger effect compared to the MICT group. Both exercise groups demonstrated a strong correlation between blood lactate concentration and BDNF/p-TAU levels ($p<0.01$) indicating that exercise intensity plays a crucial role in modulating neurochemical changes associated with AD.

Conclusion: This study underscores the potential of HIIT as a viable intervention for mitigating neurodegeneration in AD by enhancing BDNF and reducing p-TAU levels. The findings also highlight the importance of exercise intensity in achieving these neurobiological benefits and suggest a muscle/brain crosstalk interaction in response the exercise.

Keywords:*Aging. Exercise. Mental Health. Neurophysiology, Neuroscience*

1. INTRODUCTION

No human brain disorder has received more attention in recent years than AD disease (AD). AD is characterized by memory impairment, cognitive decline, and progressive dementia with altered neurochemical markers [1]. Although the role of inflammation in AD is not fully understood, exploring the connection between inflammatory factors, and myokines with the disease is important.

Muscle activity, especially during intense physical exercise, plays a key role due to its neuroendocrine regulation [2,3]. Myokines, substances released by muscles after vigorous exercise, such as lactate, interleukin-6, and irisin [4,5], are linked to brain plasticity and

function. These substances are produced from minutes to days after intense exercise and have significant effects on brain [3].

The pathophysiology of AD involves a reduction in cerebral cortex choline acetyltransferase, neurotransmitters, and neuromodulators, along with changes in their synthesizing enzymes, modifications in beta-amyloid, and alterations in neuronal morphology (Cummings et al., 2012). Reduced production of brain-derived neurotrophic factor (BDNF) and increased production of p-TAU [6] are linked to neuron and axon death in AD due to the hyperphosphorylation of TAU protein [7].

Physical activity is one of the few effective interventions for neurodegenerative diseases and other cognition- and memory-related problems, including AD [8]. Many studies reported that physical activity can counteract the neurobiological effects of AD. For example, reduced functional decline in the hippocampus [9], and improved mitochondrial health in the brain [10], both associated with improvements in many aspects of the brain as his electrophysiology, astrocyte remodeling in the long-term exercise exposition [11] could be benefited to the physical exercise. However, the intensity of the exercise intervention can make a significant difference due to the release of lactate and myokines like IL-6 and irisin [12]. For example, intense exercise can improve mitochondrial health in the brain and lead to astrocyte remodeling with long-term exposure [11]. These changes can result in important cognitive benefits, justifying the use of this approach in our study.

Previously, our group displayed that the HIIT is able to improve the cognition pf healthy adults [13], for frailty older adults [14], the glycemic control of older adults with metabolism impairments [15], and in the cognition and dementia symptoms of frailty older adults [16]. In conjunct, this allows us to explore more about the effect of HIIT in neurodegenerative impairments related to AD.

Since PMED has shown positive results in treating memory-related, cognitive, and mental illnesses more effectively than moderate or low-intensity physical exercise, this study aims to provide insights beyond traditional aerobic or resistance training. It is crucial to explore whether the intensity and type of exercise affect the efficacy of physical exercise, as this approach is poorly explored in the literature regarding the neurobiological impairments caused by AD. This study specifically aims to examine the effects of PMED on brain-derived neurotrophic factor BDNF and p-TAU in AD.

2. MATERIAL AND METHODS

2.1 2.1 Experimental Approach to The Problem

For determine the effects of physical exercise, and non-invasive brain stimulation, both in electrophysiological behavior of the brain, the executive functions, and dementia symptoms in older adults with AD we planning two exercise approach to stimuli two levels of blood lactate concentration in response to the exercise. We controlled the exercise intensity across the heart rate, and lactate. Then, we measured the BDNF and p-TAU, and performed the correlation test to determine possible influence of the this myokine and the brain chemistry.

2.2Study Type, and Participants and Ethical Statement

The study involved 1096 elderly patients with AD from several centers: Vila Vicentina Community Center (CTIV), Elderly Support Center of the University of Pará (UEPA), Senior Living Center (CCI), and SESC Puerto Velho, Brazil. However, only 88 elderly patients met all the inclusion and exclusion criteria. Recruitment was conducted by the National Institute for Disability Research (NINCDS) Recruitment Center until completion of the Participation Diagnosis.Participants were randomly assigned to groups using computer-based randomization with BioStat 5.3 software.

2.3 Procedures for inclusion and exclusion

Nurses, trained in caring for patients with mental and exacerbating illnesses, referred older patients to the study. The diagnosis of AD followed the NINCDS criteria [17] and was confirmed by the Brazilian health system. To be included, subjects needed to score between 9 and 10 on the Edmonton Frailty Scale (EFS) [18]. Exclusion criteria included depression, severe sensory deficits, or other neurological diseases. Ineligible individuals included those unable to complete tasks due to physical limitations, incapable of understanding the task content or participating in research, or unwilling to sign the informed consent form.

Following the selection process, 34 older adults with AD of both sexes comprised the final sample, randomly assigned to two groups (n= 29 each): GCP (71.22 ± 3.66 years old) (received only PMED), and GCS (70.77 ± 4.83 years old) (no intervention). All laboratory and statistical procedures were conducted in a blinded manner. After the completion of raw data collection, field researchers were no longer exposed to the data to ensure unawareness of individual or collective results until statistical processing. An independent statistician processed the data to prevent bias and enhance result confidence.

2.4 BDNF and p-TAU quantification

Blood collection was conducted by a nurse, extracting 8 mL from the brachial vein into vacuum tubes. Following collection, the blood was promptly stored at -20°C for up to 72 hours before processing. All blood samples were obtained between 7 and 8 am without prior exercise on the same day.

Assays were performed using peripheral blood samples according to the standard protocol for Peripheral Blood Mononuclear Cells (PBML) at Fiocruz-RO (Bioassay for Leishmania and Malaria Platform FIOCRUZ-RO). BDNF and TAU assays utilized a commercially available sandwich ELISA kit (Chemicon International, USA), following the manufacturer's instructions. Samples were diluted 1:2 and plated on microtiter plates (96 flat-bottom wells) with a standard curve ranging from 7.8 to 500 pg of BDNF (sensitized), incubated for 24 hours. Plates were washed four times with wash buffer and incubated with rabbit anti-BDNF antibody (1:1000 dilution) for 3 hours at room temperature.

Following washing, a second incubation with peroxidase-conjugated anti-rabbit antibody (1:1000 dilution) was carried out at room temperature for 1 hour. BDNF levels were determined by measuring absorbance at 450 nm after the addition of streptavidin, substrate, and prepared solutions. The standard curve demonstrated a direct relationship between optical density (OD) and BDNF concentration, where higher OD values corresponded to higher BDNF concentrations in the analyzed samples. P-TAU levels were analyzed using the same method as for BDNF.

2.5 Physical exercise protocols (PMED)

2.5.1 High-Intensity interval training

The entire program consists of 30-minute classes, structured as follows: 5 minutes for warm-up, 20 minutes for core exercises, and 5 minutes for technical cool-down. Participants begin in a seated position and transition between various standing positions throughout the session.

The core component of the PMED program includes exercises targeting lower body, abdominal, upper body strength and resistance, balance, and overall motor coordination. Intensity levels vary in cycles. Participants have the autonomy to pause and rest if they feel fatigued or uncomfortable, as the exercise regimen is self-regulated. The program is designed to induce fatigue, with resting indicating maximum intensity reached, ensuring a progressive and high-intensity exercise experience.

Training intensity reaches up to 80%, determined using a hypothetical repetition-maximum protocol from the American College of Sports Medicine (ACSM) (Communications et al., 2002), followed by straightforward percentage calculations. During stress tests, exercises are performed at a standardized intensity until concentric failure is achieved. New loads are adjusted based on these outcomes every two weeks. The formula used is: [20 reps at standard load * (percent work) = reps].

2.5.2 Moderated-Intensity Interval Training

Performed at 50% and 60% of maximum heart rate measured with a finger oximeter (GTECH, model LED, Brazil) in a 30 x 15 m room next to an urban network basic health unit, a walking program of 40 minutes was performed to promote the cool down, a 5-minute relaxation session was performed using very low-intensity stretching techniques similar to yoga. All maneuvers take place in a delineated, flat area of the parking lot. All possible obstacles have been removed to avoid accidents.

2.6 Statistical Procedures

Before participant recruitment, sample size and power calculations were conducted with a focus on changes in heart rate variability. The data did not exhibit a common standard deviation ($p > 0.05$). A sample size of 14 subjects per group was determined necessary to achieve at least 80% power to detect mean differences between groups. The actual achieved power was 91.3%. The power calculation method was previously described (Wedell-Neergaard et al., 2019).

Statistical analysis proceeded through three phases. First, the Kolmogorov-Smirnov test (Dallal-Wilkinson-Lille p-value) assessed data normality, confirming a parametric distribution ($p > 0.05$). Data were then depicted descriptively using mean and standard deviation plots. Second, following confirmation of normality, the Kruskal-Wallis test with Dunn's post hoc test (5% significance level) was employed to identify differences within and between groups in the post-intervention phase. The Spearman correlation test was used. All statistical procedures were conducted using GraphPad Prism 5.0.

3. RESULTS AND DISCUSSION

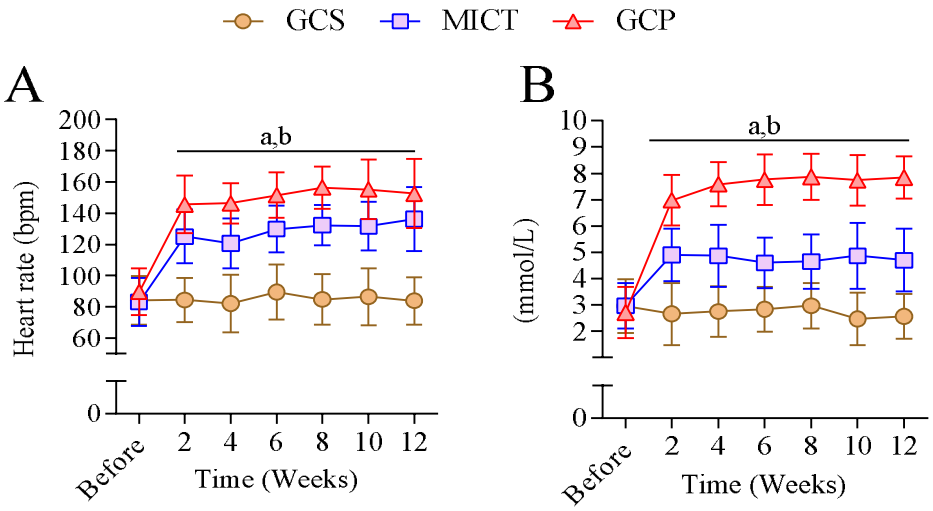
3.1 The group displayed a homogenous distribution of age, marital status, and formal instruction.

Population demographic profiles were defined using the following variables: (1) baseline mental state (MMSE), (2) gender, (3) age, (4) income, (5) social income, (6) marital status. Overall, distributions were similar between the groups for almost the entire population profile. As there were no significant differences among most of these variables, statistical checks for normality of distribution were performed only between age and baseline mental status, the only variables showing significant differences between groups. Patients were predominantly in the 65 to 70 age group (50.0%), followed by the 71 to 75 age group (36.6%) and 76 years or older (13.3%). Regarding marital status, more than half of the participants were married (67.83%), followed by divorced (16.6%) or widowed (15.0%).

3.2 The intensity control displays adequate exercise control

This study investigates the impact of high-intensity body weight interval training (PMED) on brain-derived neurotrophic factor (BDNF) and phosphorylated-TAU protein (p-TAU) in AD and the possible participation of the lactate in crosstalk phenomenon in response the intensity of the physical exercise. GCP and MICT were found to significantly increase BDNF levels and decrease p-TAU, suggesting a beneficial effect on neurochemistry related to AD pathology. Additionally, GCP overperformed the MICT. To both, the correlation test found strong correlation of the lactate. These findings highlight the potential of high-intensity exercise as a short-term treatment for neurobiological impairments in AD.

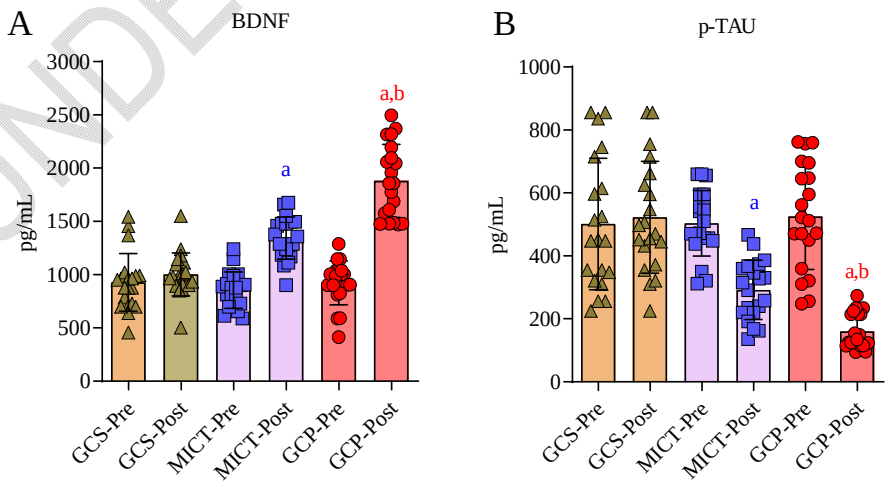
The baseline heart rate and blood lactate showed no difference between all groups (p>0.05). However, both reached the planed cardiac frequency. The cardiac frequency measured during the exercise showed differences for all data points in MICT and GCP to Before (p>0.0001). The comparison between groups displays differences between MICT and GCP (p>0.01). Similar results were found to blood lactate. Both, MICT and GCP exhibit differences to Before (p>0.0001) and between then (p>0.01). These data are summarized in figure 1A and 1B.



A and B a= $p<0.0001$ *vs* Before, b= $p<0.01$

Figure 1: Exercise Control. GCP (n=29, experimental group with AD receiving HIIT), MICT (n=29, with AD receiving walking intervention), and GCS (n=29, negative sitting control without intervention). Figure 1A= Cardiac Frequency; and 1B= Blood Lactate. The Two Way ANOVA with Tukey's Post Hoc test both set up at 5% of significance was used to identify the within-group and between-group possible difference.

Regarding BDNF variants, GCS showed no difference post-intervention (p>0.05). GCP increased post-intervention ($p<0.0001$) (Fig. 2A). Examining p-TAU (Fig. 2B), GCS values displayed no difference post-intervention (p>0.05). GCP exhibited a decrease in p-TAU (p<0.0001) (Fig. 1B). Although not necessary we performed the size effect showing large effect in regards both molecules (d= 0.92 and 0.95, respectively).



a= 0.0001 vs baseline and b= 0.01 vs MICT-Post

Figure 2: BDNF and p-TAU quantification. GCP (n= 29 AD receiving PMED), and GCS (AD n= 29, without intervention). ELISA was used to quantify BDNF and p-TAU proteins before and after the intervention. The Kruskal-Walli's test was followed by DUNN's post hoc test with a significance of 5%. **Note:** (ns= non-significant; *= *p*< 0.0001 for intragroup Pre- *vs* Post-test of GCP and the Post-test of GCP *vs* all other data points).

Previous studies have shown that exercise, including high-intensity interval training, modulates BDNF levels and enhances neuroplasticity [19]. Our results align with these findings, indicating exercise-induced BDNF release may be related to the exercise intensity (Lima et al., 2017; Silva et al., 2022) which can lead to an avenue of new approach to investigate the mechanisms under these observations. These facts, allow us to affirm that the exercise-based interventions exhibit significant positive impacts on neurochemical impairment in AD. The effect sizes observed in BDNF, and TAU protein levels underscore the relevance of these interventions. Overall, the exercise demonstrates the ability to counteract the common pathological chemical changes in the brain caused by AD contributing to the field's understanding.

3.4 The correlation test display strong correlation between blood lactate with BDNF and pTAU in response the high-intensity exercise

The analysis of the correlation between Lactate and BDNF revealed several significant relationships across different treatment groups. In the GCS group, the correlation was moderate and not statistically significant (p=0.8727). In the MICT group, the correlation was weak and non-significant (p=0.9090). However, in the GCP group, a strong positive correlation was observed (p=0.0169). The correlation between Lactate and p-TAU also showed varying results. In the GCS group, there was a moderate positive correlation that was not statistically significant (p=0.5142). The MICT group displayed a weak and non-significant correlation (p=0.1845). In the GCP group, there was a strong positive correlation, it did reach statistical significance (p=0.0323). These data are summarized in the figure 3.

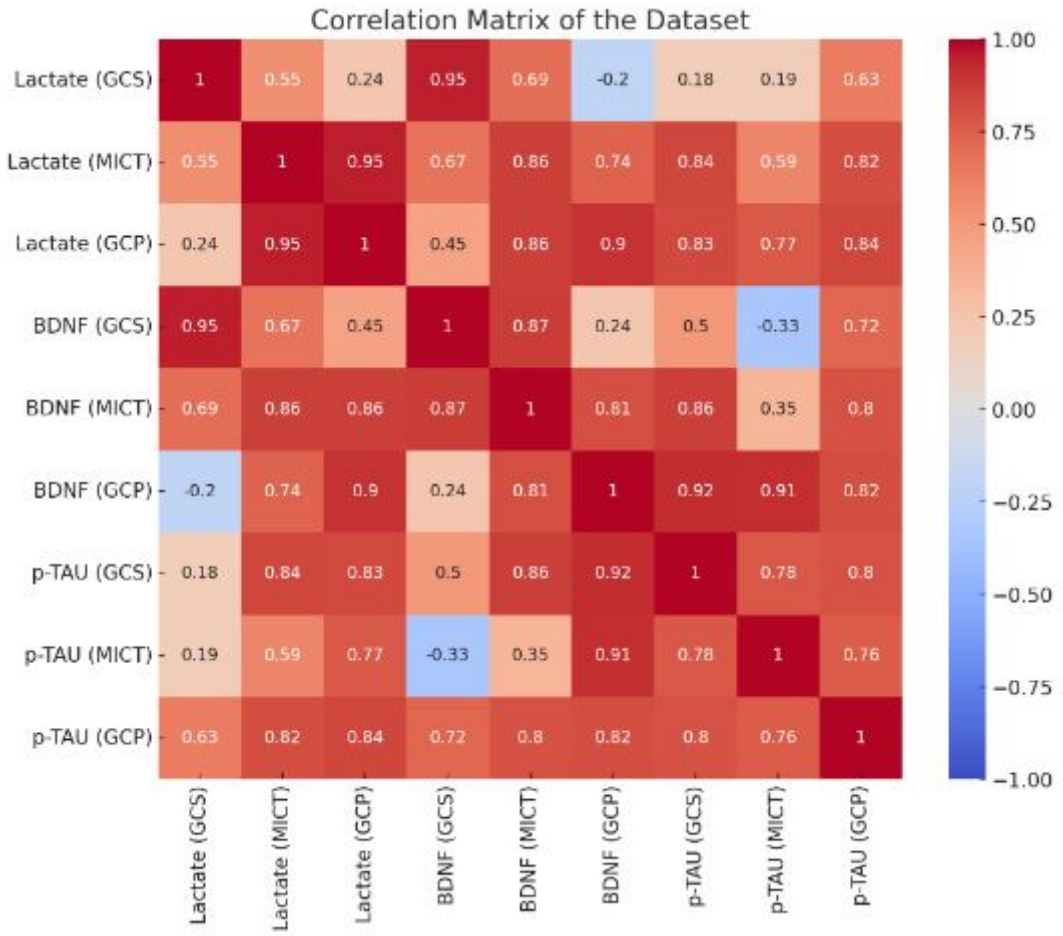


Figure 3: Correlation Matrix: GCP (n=29, experimental group with AD receiving HIIT), MICT (n=29, with AD receiving walking intervention), and GCS (n=29, negative sitting control without intervention). The Pearson Correlation set up at 5% of significance was used to determinate the possible correlation between Lactate and BDNF and Lactate and p-TAU.

To elucidate the mechanisms underlying our findings, we hypothesize that HIIT-induced changes in BDNF and p-TAU levels may be mediated through the release of lactate. Specifically, molecules such lactate are known to cross the blood-brain barrier and exert neuroprotective effects [20–22]. For instance, lactate signaling in the brain increases BDNF production, impacting brain function [23], cognition [24], long-term memory [25], and neuroplasticity [4], many of several impairments related to AD which could be an advantage to promote the physical exercise programs to fight against the AD installation and progress. The hypothesis, not investigated here is that the lactate protects against neuronal injury by activating Akt and ERK1/2 signaling pathways, contributing to the neuroprotective effects of physical exercise [12], and in the regulating JAK2/STAT3 and PACAP signaling pathways, countering NMDA-induced neurotoxicity [26,27], generating a protective molecule linked to intense exercise. In conjunct, we suppose that this molecule exported to the muscle under intense physical exercise could compose the main mechanism under the phenomenon observed.

While our study underscores the potential of HIIT in improving neurochemistry in AD, limitations warrant consideration. These include the relatively small sample size, challenges in medication control, and the absence of beta-amyloid investigation, and another myokines as interleukin-6 and irisin, two between many molecules that can be closed involved in this prosses. Furthermore, the potential influence of anti-inflammatory medications on BDNF levels necessitates careful consideration in future studies.

4. CONCLUSION

Despite these limitations, our findings support the notion that PMED-induced changes in BDNF and p-TAU levels offer promising avenues for combatting neurobiological impairments in AD. Future research should aim to elucidate these mechanisms further and explore personalized exercise protocols that optimize neuroprotective outcomes.

DISCLAIMER OF ARTIFICIAL INTELLIGENCE

The authors hereby declare that generative AI technology, CHAT GPT 4.0, was used for editing the English language of the manuscript. The request was solely to correct spelling, punctuation, and grammar, without altering, adding, omitting information or data, or changing the meaning of the text.

ETHICAL APPROVAL AND CONSENT

The accomplished all ethical parameters provided by Platform Brazil according to the National Health Council decision CNS 466/12. Registration number 2066823 was issued thereafter. In accordance with the ethical principles like the law, all volunteers and their legal representatives signed a free informed consent form before participating in this study as volunteers after
eliminating their doubts about this study.

ABREVIATIONS

AD: Alzheimer's Disease
BDNF: Brain-Derived Neurotrophic Factor
p-TAU: Phosphorylated-Tau
HIIT: High-Intensity Interval Training
MICT: Moderate-Intensity Continuous Training
PMED: High-Intensity Body Weight Interval Training

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