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Non-invasive Brain Stimulation Enhance the Physical Exercise Effect Against the Cognition Impairments and Dementia Symptoms in Alzheimer's Disease: An Experimental Controlled Trial

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Abstract: Background: Alzheimer's Disease (AD) is a progressive and incurable condition that prompts the exploration of interventions to slow its advancement and enhance the quality of life. The cortical brain waves could have a role in the process of executive function deterioration, increasing dementia symptoms. **Objective:** To interrogate 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. **Methods:** One hundred and sixteen older adults were grouped (n=22 each): GAE (AD, PMED+NIBS), GCP (AD, PMED), GCN (AD, NIBS), GCS (control, no intervention). Binaural beats were used as a non-invasive brain stimulation, physical exercise, or both, were applied during 16 weeks. Pre/post measurements included Alpha Band, and SMR Rhythms, executive functions, and dementia symptoms. **Results:** GCS showed no significant changes ($p>0.05$). GCN and GCS slightly enhanced inhibitory control ($p>0.05$) and working memory ($p>0.05$). In contrast, GCP and GAE improved executive function ($p<0.05$), reduced dementia symptoms ($p<0.05$), and modulate the brain waves. GAE's improvement outperformed GCP ($p<0.05$). **Conclusions:** The NIBS, and PMED, both have benefits on cognition and mitigate dementia symptoms in older adults with AD, however, the combination of the PMED and NIBS has synergic improved effects.

Keywords: short-term memory; electroencephalography; executive function; Alzheimer's disease. brain ageing; working memory

1. Introduction

No human brain disorder has received more attention in recent years than Alzheimer's disease (AD) [1]. Several neurobiological effects occur in the context of brain sensory and psychiatric disorders [2]. AD shows a very high prevalence of degenerative and progressive dementia [3], which is projected to increase four-fold by 2050 [4]. Neurodegeneration is often associated with cognitive problems, the most common of which are learning, cognition, and memory problems [5]. Often, cognitive dysfunction such as working memory dysfunction is the main behavioral symptom in older adults [6], and there is a lack of cures as only palliative measures and medications are used in most cases, suggesting an urgent need an alternative.

The pathophysiology of the disease is characterized by a reduction in cerebral cortex choline acetyltransferase, a number of neurotransmitters and neuromodulators, their synthetizing enzymes and the neuronal morphology that produces them [1]. Reduced production of brain-derived neurotrophic factor (BDNF), and increased production of phosphorylated TAU protein (p-TAU) together the beta Amyloid modifications (β-Amy) are the most prominent neural features of AD [7,8]. Biologically, neuron/axon death in AD is due to hyperphosphorylation of TAU protein [9]. Several manuscripts have shown that exercise attenuates TAU pathogenesis in a mouse model of Alzheimer's disease-like tau pathology [10]. TAU protein is often overexpressed in neurodegenerative diseases, including Alzheimer's disease [11] and used as a marker of severity [12], however, the biochemical parameters is not the central point of this manuscript.

Another important key of the brain function is his electrophysiological behavior [13]. In this sense different brain waves have important relationships with many brain functions as the Alpha band with the cognition [13], and the sensorimotor rhythm (SMR) with the motricity [14]. Due to this, the investigation of the brain wave behavior could be crucial to explain in part the effect of many actions against the degenerative effects of the AD.

However, data suggest that physical activity is one of the few effective interventions for neurodegenerative diseases and other cognition- and memory-related problems, including AD [15], and data suggest that physical activity is one of the few effective interventions for neurodegenerative diseases and other cognition- and memory-related problems, including AD. In addition, many studies reported that physical activity can counteract the neurobiological effects of Alzheimer's disease. For example, reduced functional decline in the hippocampus [16], and improved mitochondrial health in the brain [17], both associated with improvements in many functional aspects of the brain as his electrophysiology, astrocyte remodeling in the long-term exercise exposition [18], and, specifically our manuscript, evidence for beneficial neuroplastic effects is both related to morphological aspects of the cortex [19]. Nonetheless, obtained important cognitive benefits from resistance training, justifying the use of this type of exercise in our study [19].

Noninvasive brain stimulation (NIBS) is another form of cognitive therapy that has received attention recently [20,21]. This approach has shown promise in the treatment of AD and Parkinson's disease [22], other types of mental disorders [23], and a variety of problems associated with memory and cognition [24]. Although studies examining the effects of resistance training (PMED) and even NIBS have shown some efficacy in AD, the results of combining PMED and NIBS as an intervention in the treatment of AD have not been evaluated [20,21].

Since the independent application of either NIBS or physical exercise has revealed positive results in memory-related, cognitive, and mental illness treatment [25], the likelihood of these methods being more effective if applied in combination is relatively high, therefore, the main objective is to exam the effects of physical exercise, non-invasive brain stimulation, both in electrophysiological behavior of the brain, the executive functions, dementia symptoms.

2. Methods

2.1. Participants

The universe of recruiting was composed by 1096 elderly patients with Alzheimer's and Parkinson's from the Vila Vicentina Community Center (CTIV), the Elderly Support Center of the University of Pará (UEPA), the Senior Living Center (CCI) and SESC Porto Velho, Brazil. Syndrome and other psychiatric diseases, only one hundred and sixteen elderly patients met all the inclusion and exclusion criteria for participation in this study.

Diagnosis of dementia is made over a period of weeks by a multidisciplinary team consisting of a general practitioner, a psychiatrist, a psychologist and a nurse in all living national neuro communication parameters The National Institute for Disability Research (NINCDS) Recruitment Center works until completion of the Participation Diagnosis. About this study, the Mini-Mental State Examination (MMSE) [26,27] was used for an objective measurement before and after the intervention program.

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2.2. Procedures for Inclusion and Exclusion

Nurses trained in caring for patients with mental illness and other types of exacerbating illnesses referred older patients to the study. The diagnosis of AD follows the NINCDS [28]. This diagnosis was made by the medical or human services department of the Brazilian health system. Furthermore, previously used questionnaires confirmed the identity of these elderly patients and highlighted the characteristics of their dementia symptoms.

To be included in this study of Alzheimer's patients, subjects had to score 9 to 10 on the Edmonton Frailty Scale (EFS) [27,29]. In addition, all study participants were between the ages of 65 and 80, had an MMSE score of 11 or higher, participated substantially in an exercise program, and had physician clearance to participate in program intervention level exercise.

Volunteers were not eligible if they had depression or a clinically acceptable diagnosis of severe sensory deficits or neurologic disease syndromes. Patients who are unable to complete the research tasks due to physical limitations, patients who cannot recognize the content of the research tasks, patients who do not understand their participation in the research, and patients who do not agree to sign the informed consent form are considered unqualified. After the selection process was complete, 116 older adults [29], all with AD constituted the final sample and were randomized into four groups (n= 29 each). The first group was named as the experimental group, AD (GAE) received PMED plus NIBS, AD received only PMED (GCP) positive control, AD received only NIBS (GCN) positive control, and sedentary negative control (GCS) did not intervene. It must be said that all laboratory and statistical procedures were blinded.

Then, after the raw data is collected and sent for statistical processing, field researchers are no longer exposed to the data, so they cannot see the results from an individual or global perspective. This ensures that they do not know individual or collective results until they are statistically processed. An independent statistician was commissioned to process the data. This procedure was chosen to avoid bias and to provide a high level of confidence in the results.

2.3. Sample Characteristics

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, (7th) education and (8) time to take medication for illness. Overall, distributions were similar between the three 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. For this review, the Mann-Whitney test was adjusted for $p \leq 0.05$. Table 1 shows the descriptive characteristics of the study participants and the means of all measures, including age, MMSE and between-group comparisons.

Table 1. Descriptive Characterization of the study participants.

Variable (MEAN±SD)	**GCS (n=29)**	**GCN (n=29)**	**GCP (n=29)**	**GAE (n=29)**
Age	70.98±3.16	70.87±4.91	70.01±5.38	71.09±5.76
MMSE (MEAN±SD of Pre-)	21.16±4.18	20.89±4.67	20.91±3.99	21.02±2.29
Age *p-value*				
GAE *vs* GCP =.08	GAE *vs* GCN =.79		GAE *vs* GCS =.89	
GCP *vs* GCN =.75	GCP *vs* GCS =.71		GCN *vs* GCS =.12	
MMSE *p-value*				
GAE *vs* GC*P*=.27	GAE *vs* GCN=.32		GAE *vs* GCS=.20	
GCP *vs* GCN =.31	GCP *vs* GCS =.47		GCN *vs* GCS =.55	

Legend: The volunteers of the GAE (n=29, experimental group with AD subjected to PMED plus NIBS), GCP (n= 29, positive control with AD receiving only PMED), GCN (n=29, positive control with AD that was receiving only NIBS), and GCS (n=29, negative sedentary control kept with no interventions) groups were submitted to the Mini-Mental State Exam (MMSE) test as part of the inclusion and exclusion methodology. The results are described herein. The Mann-Whitney test was used with a significance of 5%. **Note** SD= Standard Deviation).

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2.4. Non-Invasive Brain Stimulation Protocol (NIBS)

The auditory signal synthesizer delivered stimuli at a frequency of 8-12 hertz (Hz) in a binaural firing configuration. The modulator instrument is an Orion brand manufactured by Touch Technology® (Toronto, Canada). The system works by providing brainwave modulation, thereby promoting better attention and increased capacity for mental processing [21,44]. Each step of stimulation lasted 20 minutes, and the stimulation was repeated 3 times a week throughout the ten-week intervention period, for a total of 30 sessions.

2.5. Physical Exercise Protocols (PMED)

The entire program consists of 60 minutes per class, of which 40 minutes are dedicated to physical activity, divided into 5 minutes warm-up, 30 minutes core physics and 5 minutes technical cool down. Participants start in a sitting position and then have to move to different standing positions and vice versa. The core part of the PMED program, followed by a warm-up session, includes exercises for lower body, abdominal, upper body strength and resistance, balance, and overall motor coordination; Intensity plays out in circles. To this extent, if any of the subjects felt tired or uncomfortable, they could stop and rest. While the exercise is self-regulating, all the exercise stimulation is designed to wear yourself out. If the subject required rest, we assumed the exercise was at the highest intensity level, thus allowing us to assume that the exercise program was progressive and characterized by high intensity.

Finally, the relaxation part involves practicing breathing exercises and internalizing the mind, such as those suggested by Eastern techniques such as tai chi or yoga. Resistance training was performed at up to 70% intensity, and muscle strength was determined by a hypothetical repetition-maximum protocol from the American College of Sports Medicine (ACSM) [45], followed by a simple percentage calculation. In summary, for the stress test, all selected exercises were performed at standard intensity until concentric failure. New loads were then performed until the subject reached concentric failure at 20 repetitions. Then set the exercise to 12 repetitions. Strength is recalculated every two weeks using this same method. The equation is: [20 reps at standard load * (percent work) = reps]. All intervention program was performed during 16 weeks.

The exercise intensity was controlled by the maximum heart rate reached in the end of each fourth exercise set of on-by-one exercise during the exercise session every in the Friday. The assessment was done across the Finger Oximeter G-Tech. The exercise intensity was corrected even when necessary to keep ~70% of the maximum heart rate. Additionally, the evolution in the charge was recorded. Finally, the blood lactate was acquired in the same moment that the heart rate frequency in the counter lateral finger and measured using the Accu Check Lactometer.

2.6. Cognitive and Dementia Symptoms Assessments

2.6.1. Memory

2.6.1.1. Digit Span

The Digit Span Test (DST) [30] involves testing short-term memory by verifying working memory operations. The test addresses the functional aspects of memory based on a person's ability to repeat a series of items (which can be letters, numbers, or words) in the correct order to assess the person's memory. The test features memorizing a series of numbers and/or words, with the sequence increasing in length with each correct answer. The DST application is reliable, well-validated, and cross-validated [31], showing that it is one of the most applicable tests for examining working memory function.

2.6.1.2. Short Term Memory Part of the Montreal Cognitive Assessment (MoCA)

The MoCA consists of one page, covering the cognitive domains of executive function and visuospatial abilities, naming, short-term memory, attention and working memory, language,

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concentration, verbal abstraction, and orientation. It can be carried out within 10 minutes, with a maximum score of 30 indicating no errors were made. Here, only the fifth domain of this cognitive scale, the Short-Term Memory. The Short-Term Memory Part of the Montreal Cognitive Assessment is calculated by adding the number of words remembered in free delayed recall, category-cued recall, and multiple choice–cued recall multiplied by 3, 2 and 1, respectively, with a score ranging from 0 to 15. The examiner administers a memory test by reading a list of 5 words at a rate of one per second.

Additionally, the sessions in regards the assessment of the memory of the Literacy Independent Cognitive Assessment (LICA) and the Mini Mental State Exam were used.

2.6.2. Inhibitory Control

2.6.2.1. Simple and Complex Reaction Time

The stimulus was presented in the same size of the hand and was called as "Simple Reaction Time (SRT). However, in the second, the stimulus was presented in counter lateral side of the domain hand, producing an interference in the answer and called as "Complex Reaction Time (CRP). We performed five executions for acclimatization and more 50 for assessment.

2.6.2.2. Stroop Test

For the third cognitive assessment, the inhibitory control assessment, part of the Stroop test was adapted to a two-choice motor reaction time task format previously used by our group [33,34]. For this assessment, subjects had to press a computer button as soon as a light (stimulus) appeared on either side of the computer screen. Final averages were calculated for five of each part of the 30 trials. There is scientific evidence that reaction time is an important component of human functioning and mental health, especially in older adults [35,36]. Furthermore, several studies analyzing this factor have shown that older adults can significantly improve their responses to such tests through regular practice [37–40]. Additionally, an electronic reaction time test was used in two versions. First, the simple reaction time, with the computer-gaming reaction test designed to evaluate the reaction time to frontal visual stimuli. The testing was carried out with dominant hands, five executions for acclimatization and more 50 for assessment. The instructions were, when the red box turns green, click as quickly as you can.

2.6.3. Mental Flexibility

2.6.3.1. Trail Making Test to Assess the Mental Flexibility

The Trail Making Test consists of two parts, each with 25 circles spread across a sheet of paper. In Part A, the circles are numbered from 1 to 25, and the individual is tasked with connecting them sequentially. Part B includes both numbers (1 to 13) and letters (A to L), requiring the participant to connect them alternately in an ascending pattern (e.g., 1-A-2-B-3-C). The goal is to complete the trails as quickly as possible without lifting the pen or pencil. Errors are noted and corrected immediately, with correction time factored into the overall completion time. If both parts are not completed within five minutes, the test is discontinued. The procedure involves providing the patient with the test sheet and a writing implement, demonstrating the task, timing the completion of both parts, and recording the results. Scores are reported in seconds, with higher scores indicating greater impairment.

2.7. Cognitive Screening and Dementia Symptoms

2.7.1. Mini Mental State Exam (M.M.S.E.)

The MMSE has been validated in Brazil and its content is divided into seven categories. Each category is designed to assess a specific cognitive function, with scores ranging from 0 to 30; higher scores indicate better cognitive function. Considering the influence of educational factors, values of

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18 (average educational level) and 26 (high educational level) are generally defined as critical values [21,32].

2.7.2. Montreal Cognitive Assessment (MoCA)

The MoCA consists of one page, covering the cognitive domains of executive function and visuospatial abilities, naming, short-term memory, attention and working memory, language, concentration, verbal abstraction, and orientation. It can be carried out within 10 minutes, with a maximum score of 30 indicating no errors were made. Scores were corrected for low education according to instructions, by adding one point to the total score of patients with 12 years of education or less. The original suggested cutoff for the diagnosis of CI was a score of (below) 26 (less than 26).

2.7.3. Literacy Independent Cognitive Assessment (LICA)

The LICA in its finalized form presents a 300-point examination, comprising 13 distinct assessments targeting memory, visuospatial acuity, executive function, attention, linguistic prowess, and computational skills. The narrative recall segment entails immediate recollection, delayed retrieval approximately 20 minutes later, and subsequent recognition. Meanwhile, the word recall segment incorporates three successive learning trials featuring ten nouns each, followed by immediate recall, a recall trial after a 20-minute interval, and recognition. Assessing visuospatial prowess and memory involves replicating and identifying ten stick formation images, derived from adaptations of the Stick Pattern Reversal Test. Evaluation of executive functions encompasses the Digit Stroop test and a task gauging fluency in animal naming. Attention, concentration, and working memory are scrutinized through forward and backward repetition tapping exercises involving nine Corsi blocks. Modifications to the arrangement of the blocks on the board and the tapping sequences were made in line with adjustments to Corsi's original block-tapping paradigm. Language assessment entails a fifteen-item confrontation naming challenge encompassing animals, fruits, and vegetables, alongside the previously mentioned fluency task. The Color and Object Recognition Test (CORT) underwent alterations derived from semantic comprehension assessments concerning the visual morphology and hues of various objects. Lastly, computational aptitude is subject to evaluation.

2.8. Brain Wave Patterns Assessment

The assessment of the brain's electrical activity is performed using an EEG, which records activity at specific points in the brain's cortex in real time. The EEG used was produced by Neurotec do Brazil® model Neuromap EQSA260 (São Paulo, Brazil). All cranial points evaluated were selected according to the international system recommended by the Brazilian Neurophysiological Society [41]. The instrument's terminals are secured in such a way that it is grounded to avoid any type of electrical interference during data collection (DA Silva *et al*, 2016).

The focus here is on alpha-band assessment of the frontal cortex and verification of SMR rhythms in sensorimotor areas. This is due to the relationship between alpha bands on frontal lobe structures recorded primarily by C3 and C4 electrodes and cognition according to Jasper's International System 10-20 [41]. A major interest related to SMR rhythm is the function of this specific region.

Data were processed using Brain Vision Analyzer Software® (version 2.0, Brain Products, Gilching, Germany). First, the data is down sampled to 250 Hz. ECG pulse artifacts were measured using Allen et al. [42]. In a nutshell, intervals are automatically scored based on repeating patterns, intervals are calculated, and their average is subtracted. After the ECG risk model was created, the ECG trace data was removed. Filter the data using high-pass and low-pass filters (0.5 to 70 Hz each) and apply a notch filter at 50 Hz. Using visual data leakage removes possible interference in the channel and any interpolation of such interference to the eye, which is often identified as a target for finding data distortions. Re-reference the EEG signal to a standard reference point by the arithmetic mean of the electrophysiological activity at the peak power of F3, F4, C4, and CZ. Extraction is performed using a sophisticated demodulation technique that correlates to EEG temporal traces in the full alpha band (8-12 Hz), lower (8-10 Hz) and upper (10-12 Hz). Data were extracted individually and exported to MATLAB® (Mathworks, Sherborn, MA, USA) to build statistical models. These programs were previously published by Brueggen *et al*., [43].

2.9. Study Type and Research Ethics

The study is clinical, randomized, experimental in nature and underwent an ethical assessment by Platform Brazil according to the National Health Council decision CNS 466/12 for approval according to the CAAE Helsinki without declaration. Registration number 2066823 was issued thereafter. In accordance with the ethical principles similar to 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.

2.10. Statistical Procedures

Before recruiting participants, sample size and power calculations were performed based on changes in working memory performance significance and dementia symptoms among the four groups most critical to the null hypothesis. The distribution does not follow a common standard deviation (p>0.05). A sample size of 14 subjects per group was required to obtain at least 80% power to detect mean differences between groups. The actual performance is 91.3%. The method of power calculation was previously described [46].

Statistical analysis followed three distinct phases. First, we used the Kolmogorov-Smirnov test (Dallal-Wilkinson-Lille value of p) to determine data normality, which turned out to be parametric ($p > 0.05$). Data are descriptively plotted against the mean and standard deviation of the scores. Second, after ascertaining the normality of the data distribution, according to the results obtained in the preliminary results received by older people, the Kruskal-Walli's test with DUNN's post hoc or 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. All statistical procedures were performed in GraphPad Prims 9.1.

Finally, the effect size for each intervention type was calculated using Cohen's ʆ-test for three or more interactions and for two interactions using Cohen's d-test. For this test, calculated differences between one score set and another ($ʆ^2$) between 0.02 and 0.14 are described as small effects; and $ʆ^2$ between 0.15 and 0.34 are described as moderate effects, values > 0.35 $ʆ^2$ is considered a large effect. According to Cohen's results, d is between 0.20 and 0.39 for small effects, between 0.40 and 0.79 for medium effects, and 0.80 or greater for large effects.

3. Results

3.1. The Group Displayed a Homogenous Distribution of Age, Marital Status, and Formal Instruction

The groups displayed a homogeneous distribution concerning age, marital status, and formal education. Most patients were in the 65 to 70 age group, with similar distributions across marital status and other demographic variables. Patients were predominantly in the 65 to 70 age group (30 years; 50.0%), followed by the 71 to 75 age group (11 years; 36.6%) and 76 years or older (8 years; 13.3%). Regarding marital status, more than half of the participants were married (41; 67.83%), followed by divorced (10; 16.6%) or widowed (9; 15.0%). Other demographic variables also showed similar distributions across groups (Table 2).

Table 2. Demographic distribution of the sample.

Variables		GCS	GCN	GCP	GAE
		Number of individuals in each group			
Age (Years)	65-70	18	19	18	20
	71-75	08	06	05	05

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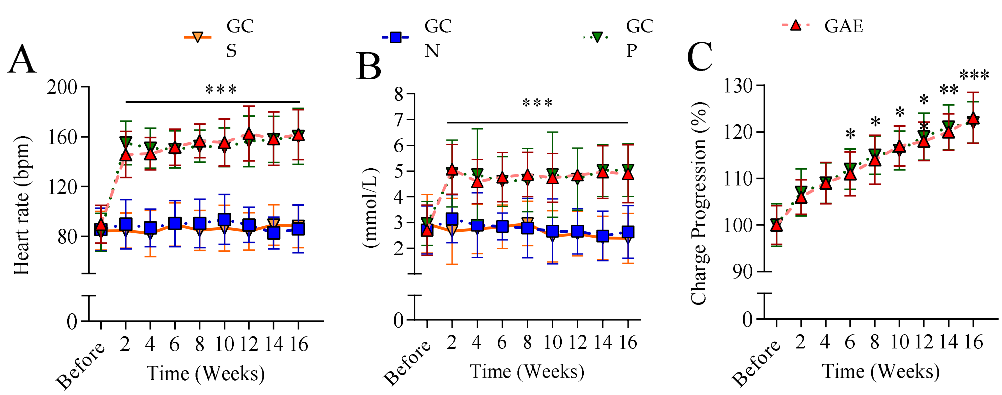
	76 >	03	04	06	04
Sex	Men	16	15	18	16
	Women	13	14	11	13
Marital Status	Divorced	14	12	16	15
	Married	14	15	10	13
	Widowed	01	02	03	01
Educational Level	High School complete>	19	18	17	17
	High School incomplete >	07	10	08	09
	College complete >	03	01	04	03
Social Income	Minimum Wage or <	09	07	08	07
	1-2 Minimum wage(s)	11	10	07	09
	2-4 Minimum Wages	03	05	06	08
	5 > minimum wage	06	07	08	05
Duration of the disease	1 year or less	-	15	13	14
	1 year or more	-	07	08	09
	2 years >	-	07	08	06

Legend: The volunteers of the GAE (n=29, experimental group with AD subjected to PMED plus NIBS), GCP (n=29, positive control with AD receiving only PMED), GCN (n=29, positive control with AD that was receiving only NIBS), and GCS (n=29, negative sedentary control kept with no interventions) groups were submitted to the MMSE test as part of the inclusion and exclusion methodology. The combination of the NIBS plus PMED enhanced working memory function, and inhibitory control, and decreased the symptoms of dementia.

3.2. The Exercise Control Showed no Difference Between the Training of the Groups

The heart rate control showed no difference between GCP and GAE (p>0.0001), however, both reached the planed cardiac frequency. The lactate level, collected exactly in the same time of the cardiac frequency display homogeneity of intensity between GCP and GAE without differences (p>0.0001). Finally, the charge progression exhibits a comparable implementation of the intensity from the sixth week. However, between GCP and GAE exhibit with no differences between them (p>0.05). In conjunct, this data shown homogeneity of the training intensity and evolution during the exercise program intervention. The figure 1 dysplay the physical exercise control.



A and B *= p<0,05 *vs* baseline **= p<0.01 ***= p<0.0001 *vs* Before, GCS and GCN. C
*= p<0,05 *vs* baseline **= p<0.01 ***= p<0.0001 *vs* Before

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Figure 1. Exercise Control. One hundred and sixteen older adults were grouped (n=22 each): GAE (AD, PMED+NIBS), GCP (AD, PMED), GCN (AD, NIBS), GCS (control, no intervention). The ANOVA TWO WAY with Tukey's Post Hoc Test set up at 5% was used.

The combination of NIBS plus PMED display a synergic effect on the cognition a dementia of older adults with Alzheimer's disease.

The GAE, subjected to the combination of NIBS and PMED, showed significant improvements in working memory, outperforming the other groups. The observed effects indicate a significant difference between GCP and GAE, suggesting that the combined intervention had a more substantial impact on working memory and in the short term memory. In terms of group comparisons, GAE showed differences across all groups ($p < 0.05$), with a large effect size between GCP and GAE ($d = 0.92$ and 0.95, respectively).

The GAE group exhibited notable improvements in inhibitory control compared to the other groups, indicating positive effects from the combined intervention on this cognitive function. Suppressed control data for GCS showed no significant change after the intervention. GCN scores also showed no difference ($p > 0.05$). However, GCP and GAE both showed significant differences after the intervention ($p < 0.05$). Between-group analyses indicated no differences in GCN, GCP, and GCS ($p > 0.05$), GCP versus GCN ($p < 0.05$), and GAE versus GCN and GCP ($p < 0.05$). Effect size tests showed a small effect for GCN and GCP ($ʃ^2 = 0.012$ and 0.014, respectively), while GAE showed a large effect ($ʃ^2 = 0.77$).

There was a significant reduction in dementia symptoms in the GAE group compared to the other groups, indicating the effectiveness of the combined intervention in improving overall dementia symptoms. In terms of dementia status, GCS showed no significant change after the intervention. GCN also showed no significant difference ($p > 0.05$). However, GCP and GAE both showed significant improvements ($p < 0.05$). Comparisons between groups showed differences between GCP and GAE compared to all other groups ($p < 0.05$), with GAE showing significant differences compared to GCP ($p < 0.05$). Cohen's test indicated large effect sizes for GCP and GAE ($d = 0.73$ and 0.94, respectively). The figure 2 display the data related the gocnition and demantia symptomns.

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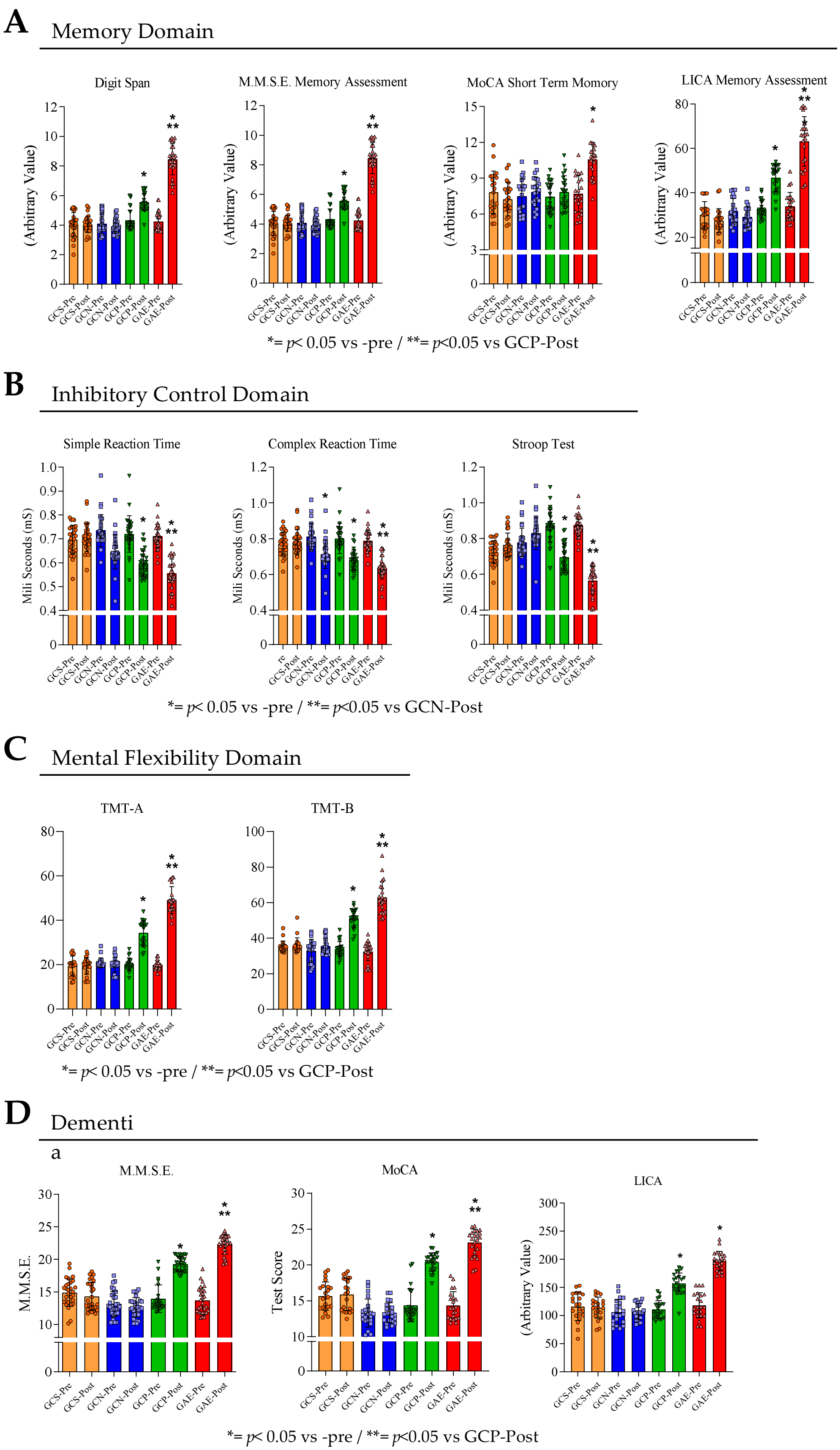

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Figure 2. Mental parameters. One hundred and sixteen older adults were grouped (n=22 each): GAE (AD, PMED+NIBS), GCP (AD, PMED), GCN (AD, NIBS), GCS (control, no intervention). The ANOVA TWO WAY with Tukey's Post Hoc Test set up at 5% was used.

3.3. The NIBS, and PMED Interventions Both Enhanced the Alpha Brain Wave and SMR Rhythm in the Pre-Frontal Area

GAE showed a significant increase in alpha wave activity after the intervention, suggesting a positive effect of the combination of NIBS and PMED. The observed effects were particularly pronounced compared to the control groups. The alpha band of GCS showed 8.69±0.47 mV at baseline and 8.83±0.46 mV after intervention ($p > 0.05$). GCP showed 8.65 ± 0.51 mV at baseline and 8.71±0.52 mV after intervention ($p > 0.05$). However, GCN changed from 8.52±0.46 mV at baseline to 13.45±1.54 mV after intervention, and GAE changed from 8.38±0.39 mV at baseline to 34.81±4, 25 mV after intervention, with significant differences ($p < 0.0001$). Regarding the effect size between groups associated with the alpha band, Cohen's d shows a small effect for GCN (d=0.27) and a large effect for GAE (d=0.97).

All groups undergoing NIBS and PMED demonstrated significant increases in SMR rhythm, indicating positive neurophysiological modulations associated with the intervention. Again, the GAE group stood out with more expressive effects. For SMR rhythms, GCS was 12.60±0.54 mV at baseline and 12.71±0.62 mV after intervention, no difference ($p > 0.05$). However, GCN increased from 12.94±0.58 mV at baseline to 15.21±0.57 mV after intervention, GCP showed 13.06±0.75 mV at baseline and 15.78±1.83 mV after intervention, and finally GAE increased from 12.69±0.42 mV at baseline All of these modifications were significantly different ($p < 0.0001$) to 15.24±0.49 mV post-intervention. Regarding effect sizes between groups, GCP, GCN, and GAE showed moderate effects ($ʃ^2$ = 0.017; 0.033 and 0.028, respectively). The figure 3 displays the brain wave paterns.

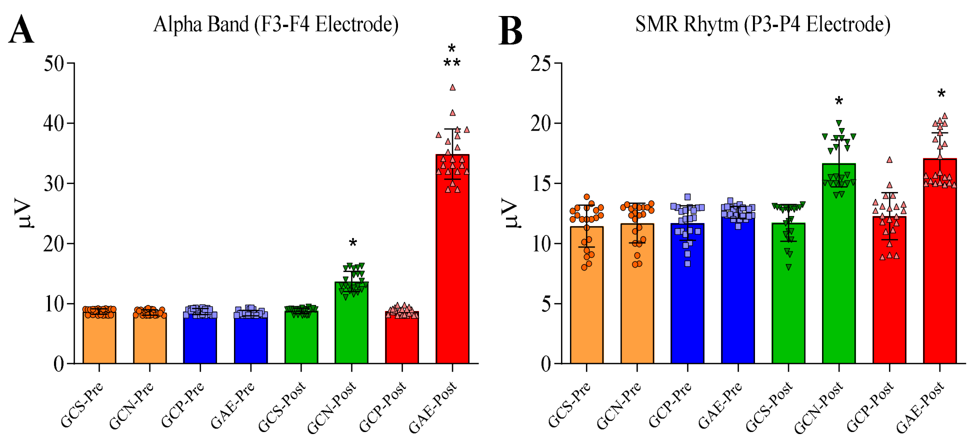

Figure 3. Electrophysiological brainwave. One hundred and sixteen older adults were grouped (n=22 each): GAE (AD, PMED+NIBS), GCP (AD, PMED), GCN (AD, NIBS), GCS (control, no intervention). The ANOVA TWO WAY with Tukey's Post Hoc Test set up at 5% was used.

4. Discussion

We present the results of a 16-week intervention of physical training (PMED) combined with non-invasive brain stimulation (NIBS) in patients with Alzheimer's Disease. Overall, individuals in the target intervention group outperform the individuals who received only physical exercise, or non-invasive brain stimulation. Furthermore, to explain possible mechanisms underlying the observed behaviors, we assessed brainwave parameters related to AD, cognition, and dementia symptoms. In this trial, the intervention proved beneficial for the primary outcome (dementia

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symptoms and cognition) and the secondary outcome (Brain wave) in those individuals who received the full intervention. This finding is consistent with our previous study in different groups, as frail elderly [47].

Previously, we demonstrated that the combination of NIBS with PMED was able to improve the cognition concomitantly the modulation of the brain waves of older people with mental and physical frailty [47]. Here only the combined intervention (PMED plus NIBS) improved working memory, which is the most evident impairment of Alzheimer's disease [47]. These results suggest that it is possible to apply this approach to combat the neurobiological impairments of Alzheimer's disease, as was done here.

For the demographic characteristics of the volunteers, age, and education presented a very even distribution, suggesting that this distribution did not negatively affect the results. In fact, the data presented in Table 1 suggest that demographics do not affect the results. For WM, GAE, and GCP showed significant improvements within and between groups in the post-intervention test (Fig. 1A); however, greater gains were obtained in GAE. No improvement was seen in the other two groups. Given that GCPs and GAEs received the same exercise regimen, these results partially support the evidence that physical activity can improve WM in AD patients [32]. While this is true, exercise associated with NIBS was more effective as GCN received NIBS but did not show improvement in WM. Nonetheless, other previous studies have shown that physical activity can improve working memory [63,64].

Here we demonstrate that the physical exercise was very well controlled and the markers used displayed the same results along 16-weeks of intervention. The increased intensity was comparable between both. In conjunct, this results suggests that the physical exercise wasn't an intervenient factor in this work, and, the NIBS was the difference in intervention between GCP and GAE.

Physical activity has benefits in various aspects of cognition, such as executive function, working memory, and learning, and may stimulate structural and functional plasticity in the brain [48]. Previous studies have shown that regular physical activity can reduce neurological risk factors such as dementia [49], Parkinson's disease [50], frailty [51], and AD [52], which improve the quality of life [53]. Increased expression, secretion and downstream signalling of neurotrophic factors (BDNF, VEGF, IGF-1), reduced inflammation [54], and cardiovascular improvement, such as reduced arterial stiffness and lowered blood pressure [55–58], and cardiovascular improvement, such as reduced arterial stiffness and lowered blood pressure [57,59] are some of the mechanisms that could explain exercise-induced neuroplasticity. Taken together, all of these effects can contribute to the development of positive brain health, as shown in numerous studies [60–62].

Another fact has to do with the type of exercise regime implemented. For example, we use moderate-volume, and intensity resistance exercises. This choice was made for the safety of our older volunteers, but on the other hand, studies have shown that WM is very sensitive to training intensity [34,65,66].

In regards the primary outcomes, the duration of the intervention proposed was sufficient to produce the expected changes in WM for these groups. For GCP, and GAE this time frame was sufficient to show significant gains of the same variables in the post-intervention test, highlighting the additional effect of the NIBS procedure on the same training schedule for GCN and GAE, suggesting that non-invasive brain stimulation may enhance WM.

In consonance to the results related to working memory, which is the more important clinic symptom of the initial Alzheimer's disease, GCN, GCP and GAE improved their performance on a post-intervention test assessing inhibitory control, however, GCN improved only in Complex Reaction Time test. The mental flexibility, only was affected in exercised group, but, as observed in regards the WM, the NIBS increased the exercise effect. The results about the GCP and GAE were expected, especially given that most participants initially exhibited dementia symptoms at levels of severe cognitive deficits. These results confirm other works showing the power of exercise to improve inhibitory control[67–70]. Also, there is one more thing to consider about these big improvements reported here. For example, inhibitory control, and mental flexibility are considered part of the

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overall cognitive system and represents a partial benefit of the interventions proposed here, as evidenced by current literature [34,67].

The MMSE indicates dementia status in each group. Compared with the scores defining the risk cut point for severe cognitive impairment, the only group that changed from moderate to low likelihood was GAE. Even at the lower limit of GAE scores, the other three groups remained in positions indicating a moderate likelihood of dementia with high cognitive impairment. None of the groups achieved this risk-free status for dementia, however, GCP and GAE groups had benefits from respective interventions to minimize them. Observations of inhibitory control, working memory, and mental flexibility, suggest well-known improvements in cognitive function, especially through motor regulation, which is almost always impaired in AD [52,71].

A comparative analysis of the effects of the two types of interventions on the three cognitive variables examined here showed that the GAE outperformed the other groups almost exclusively with respect to the NIBS procedure. This became apparent in tests of working memory, inhibitory function, and mental flexibility where GAE showed the most pronounced difference compared to the other groups. The impact of this type of PMED on WM is not new, and has been shown before [20,21,50,61], but with the addiction of NIBS the effect of the exercise was improved.

The secondary outcome is related to then electrophysiological activity of the brain. Gather specific observations of the frontal, prefrontal, and sensorimotor areas for their relationship to higher cognitive functions, and motor skills integrated through the intervention, both of which play a role in one factor and often impaired during dementia. Comparing them with the mean EEG of cortical regions activated by alpha waves and SMR rhythms allowed verification of changes in the activation patterns of these regions associated with each intervention type.

First, alpha wave showed an increase in absolute power output after GAE interventions. Given that these groups underwent PMED, the highest alpha-band patterns obtained by GAE were due to the additive effect of the NIBS procedure, as previously shown by our group [21,50,72] and other authors [73–75]. However, if it is related to exercise, it is reasonable to be certain that there is a potential synergistic effect due to the strongest activation of this wave in the brains of GAE subjects, who showed higher activity in this region, with a significant impact on neurophysiological craving in older adults tends to exhibit lower alpha during neurological damage caused by Alzheimer's disease [76]. Indeed, brain activation in response to physical activity has previously been shown to mediate in relation to learning and motor function [73,75], as a modulatory effect related to learning, and motricity [21,44,50] and cognition [67,77] were previously described.

Second, regarding the SMR rhythm patterns of GCP, and GAE, it can be seen that the effect after the intervention was different for all groups, as the sensorimotor areas were now more active post-test compared to pre-test. SMR rhythmic activation patterns through relevant cortical points were modified for GCP, and GAE in the post-intervention assessment. For GCP, the spectrum associated with SMR rhythms showed high activation in regions of both hemispheres (P3 and P4). These results may be related to the improvement in inhibitory control and, when combined with the alpha-band power output observed in the C3 and C4 electrodes, confirm that the improvement in brain activation may be related to the cognitive and motor improvements observed here.

These changes benefited all three groups, with effects consistent with their performance on tests assessing abilities related to the cognitive variables studied here. Thus, the superior performance of the GAE over the other groups, especially in the assessment of cognition, reflects the optimal intervention facilitated by the combination of the NIBS procedure and the PMED procedure.

What does this article add? Results associated with GAE seemed consistently more valid and beneficial than those associated with GCP, and these groups accepted either protocol used. This suggests that the combination of NIBS plus PMED, rather than alone, has been shown to improve cognitive function and brain activity in the older adults who participated in this study. The fact that the combined effect can be interpreted as an additive result of each protocol relative to the other is supported by the expansion of the effect size indicated in the Coen’s test results. Therefore, we can consider our results very promising as they identify an emerging tool that can be used as a potential adjunct in the treatment of certain neurobiological impairments caused by AD.

Although our study is quite important in terms of its results, it has some limitations. First, the sample size of the study was relatively small, although other studies of such special populations have used smaller sample sizes in each group. Second, we cannot tightly control the use of medications that may affect cortical neuromodulation, such as general anxiolytics and sedatives, because information about them is "truncated" by many older adults with AD. Third, the investigation of the BDNF, phosphorylated-TAU, and β-Amyloid can explain and give support to our results. In addition, anti-inflammatory drugs can alter the organic inflammatory state normally associated with higher levels of BDNF and thus alter the biochemical regulation of the brain. If properly controlled, these limitations can increase the ability to enable other studies using the same protocol used here.

Addressing the critical aspects of personalization and time efficiency is an advantage. The challenge of adhering to recommended exercise durations due to time constraints can be overcome through personalized programs with flexible timing. HIIT, known for its effectiveness and time efficiency, emerges as a solution for such scenarios. Introducing this time-efficient exercise method to frail individuals holds promise for efficiently enhancing cardiac or cognitive health in the elderly.

5. Conclusions

Our primary findings suggest that an intervention approach comprising PMED and NIBS improves the cognition, and alleviates the dementia symptoms in older adults with early-stage Alzheimer's disease. Furthermore, these enhancements may be linked to improved neurological function in the studied older adults. Finally, the statistical effect sizes of PMED and NIBS applied to enhance cognitive and brain activity functions revealed synergistic effects, suggesting counteraction of AD's pathological effects on certain central nervous system functions.

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