

Dual-Task Training with Cissal Stimulation Affect Cognitive and Physical Performances and Brain Wave Ratio of Patients with Alzheimer's Disease: A Randomized Controlled Trial

Elnaz Parvin

Kharazmi University

Fatemeh Mohamadian

Tehran University of Medical Sciences

Sadegh Amani-Shalamzari (✉ amani_sadegh@khu.ac.ir)

Kharazmi University <https://orcid.org/0000-0002-3021-8970>

mahdi bayati

Sport Sciences Research Institute

Behnaz Tazesh

Tehran University of Medical Sciences

Research

Keywords: Alpha wave, Theta wave, Dementia, Exercise, Cognitive performance

Posted Date: August 26th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-64074/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: This study aimed to investigate the effect of a 12-week period dual-task training on cognitive status, physical performance and brain waves of patients with Alzheimer's disease (AD).

Methods: Twenty-six AD patients were randomly assigned to two groups, training group (TG) and control group (CG). TG executed progressive combined exercises with visual stimulation twice a week for 12 weeks. Training included muscle endurance, balance, flexibility and aerobic exercises with eyes closed and opened. Brain waves on EEG and a series of physical, cognitive and mental tests were taken prior and post intervention.

Results: There was a significant improvement after training protocol in cognitive function, particularly in short-term memory, attention, working memory and executive function ($p < 0.01$). In addition, there were substantial improvements in depression status (GDS scale), aerobic fitness (6 min walking), flexibility (chair sit and reach) functional ability (chair stand, timed up and go test), strength (knee extensions, preacher biceps curl, handgrip) in TG compare to CG. These progresses was associated with significantly increase ($p < 0.05$) in the frequency of brain waves and decreased in the theta/alpha ratio.

Conclusions: In addition to physical performance, the regular combined training with visual stimulation improve brain health as indicated by improving cognitive function and reducing the theta/alpha ratio.

Trial registration: Iranian Registry of Clinical Trials, IRCT20190504043468N1.

Background

Alzheimer's disease (AD) is a chronic neurodegenerative disease, without any known treatment. This disease progressively destroys brain structures, such as the hippocampus and entorhinal cortex, due to the accumulation of pathological forms of amyloid plaques and neurofibrillary tangles (1). Consequently, mental functions, including memory and cognition, are lost, leading to a decline in activities of daily living (2). In this regard, Burns et al. (2010) reported that reduced lean body mass in AD is associated with brain atrophy and declined brain function, including cognitive performance (3).

The electrical activity of the cerebral cortex (brain waves) can be recorded via electroencephalography (EEG) by placing electrodes on the scalp. The frequency of brain waves change in AD patients, compared to older individuals or those with mild cognitive impairments (MCIs), considering a decrease in alpha and beta power (4, 5) and an increase in theta power (5, 6). These changes are associated with altered cerebral blood flow, cognitive function (7), and occipital grey matter density (8). The theta/alpha ratio (9), which is a marker of AD and cognitive disorder, increases in patients with AD, compared to healthy individuals. In patients with MCI, occipital alpha slowing may lead to AD (8). Also, the degree of reduction in alpha and beta peak frequencies is correlated with the stage of AD (4, 6). These changes can lead to depression in AD patients, and finally, result in dementia.

Epidemiological evidence suggests exercise training as a non-pharmacological approach to protect against AD (10, 11), increase the hippocampus size (12), and increase brain neurogenesis (13). These structural changes are associated with functional improvements, such as improved independence and cognition of AD patients (11). Moreover, these exercise-induced brain changes are associated with alterations in the power of brain waves. However, to the best of our knowledge, there are no studies investigating the effects of physical training on the frequency of brain waves in AD. In this regard, Gutmann et al. (2015) reported that the individual alpha peak frequency remained unchanged after four weeks of moderate exercise training in healthy individuals (14). Also, researchers have reported that acute bouts of exercise increase the power of beta waves in the frontal and central areas of the brain, which may indicate an increase in cortical activation (15, 16); however, the long-term effects of physical training are unclear.

Researchers have shown that brain activation during exercise (a dual-task exercise) is beneficial for cognitive function (17, 18). Generally, training with eyes closed and remembering to do specific exercises with several stations are simple mental activities. In this regard, Hutt and Redding (2014) showed that an eyes-closed dance training increased the dynamic balance of ballet dancers (19), as closing the eyes led to a shift from visual to proprioceptive dependence for balance control. Moreover, researchers have found that closing the eyes activates different areas of the brain, especially the amygdala, which is involved in memory and learning (20, 21).

According to some researchers, unlike other waves, the power of alpha waves increases in a resting state with the eyes closed (22), whereas it differs when the person focuses on performing activities with the eyes closed. Dual task exercises can be used to maintain the brain structure and function and improve physical independence in AD patients. Accordingly, eyes-closed exercises can activate the brain areas involved in memory to focus on activities; they may also increase alpha and beta rhythms.

Overall, AD causes disorders in different physical and mental functions. To the best of our knowledge, this is the first study to assess the effects of combined physical training with visual stimulation on the physical and cognitive functions of patients with AD. It is known that the power of brain waves reflects brain changes and that AD increases the theta/alpha ratio. Accordingly, we hypothesized that physical training combined with mental challenge could modify the power of brain waves. In this study, we aimed to investigate the effects of combined training with visual stimulation on the theta/alpha ratio, as well as cognitive and physical health of patients with AD.

Methods

Study design

This randomized clinical trial, with control and parallel groups, phase two, and single-blind design was conducted on patients with AD. We aimed to investigate the effects of a 12-week, low-intensity training, combined with visual stimulation, on the brain waves (alpha, beta, and theta), cognitive and physical

performances of patients with AD. One week before the study, the participants and their caregivers attended three familiarization sessions, where they were informed about the benefits and potential risks of the study, signed a consent form, and participated in pretests. The block randomization method was applied prior to the study, and the participants were assigned to two groups, including the training group (TG) and the control group (CG). Brain waves, psychological and cognitive status, and physical fitness parameters, including body composition, aerobic capacity, muscle strength, flexibility, and functional abilities, were assessed in familiarization sessions.

Participants

Patients with AD, who were eligible to participate in this study, were recruited from the memory clinic of Roozbeh Hospital in Tehran, Iran. AD patients, with mild dementia and the ability to walk and move independently, were included in this study. A neurologist confirmed the diagnosis of dementia, based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. Brain imaging and laboratory tests were performed to exclude other causes of dementia. The AD severity was determined, based on the Functional Assessment Staging Test (FAST).

The patients' medications, including choline esterase inhibitors (rivastigmine and donepezil), memantine, and selective serotonin reuptake inhibitors (SSRIs including sertraline, citalopram, and trazodone), were reviewed before recruiting the patients in the study. The medications were not changed during intervention in terms of type or dosage. Before entering the study, all patients received cardiac consultation to rule out possible cardiac diseases or ischemia. Patients with serious cardiac diseases (e.g., unstable angina and recent myocardial infarct) were excluded.

Of 32 eligible volunteers, the data of 26 patients (age: 67.4 ± 8.8 years; height: 165.8 ± 7.8 cm, body mass: 72.7 ± 11.3 kg, BMI 26.5 ± 4.3 kg/m²), who completed the pre- and post-tests, were finally analyzed. The participants were randomly assigned into two groups, including the training group (TG) and the control group (CG), based on their cognitive performance. A CONSORT flow diagram of the present study is shown in Fig. 1. On the other hand, the exclusion criteria were as follows: 1) deterioration of health condition; 2) inability to perform training; 3) lack of interest in continuing training; 4) not completing the posttest; and 5) the physician's decision to exclude the participant from the study. To estimate the number of participants in each group, a sample size calculation was performed using G*Power Software version 3.1.9.6 (Düsseldorf, Germany) (23) for repeated measure ANOVA, using a rejection criterion of 0.05 and 0.8 (1-beta) power, and large effect ($f = 0.5$), a minimum of 13 participants need to each group. All research procedures were approved by the Ethic committees for Sport Sciences Research Institute of Iran (approval number: IR.SSRI.REC.1398.037) and were conducted in accordance with the Declaration of Helsinki. The study has been registered in the Iranian Registry of Clinical Trials (IRCT) (one of the Primary Registries in WHO Registry Network) with registration number: IRCT20190504043468N1.

Figure 1 near here

Measures

Before and after training, the participants underwent a series of tests. All training sessions and tests were performed at Roozbeh Hospital Medical Center under the supervision of a sports medicine physician.

Cognitive status

The Montreal Cognitive Assessment (MoCA) test, developed by Nasr al-Din et al. for MCI and dementia, evaluates different domains of cognitive functioning. The reliability of this test was 92%, based on Cronbach's alpha, and its internal consistency (IC) was 83% (24). The maximum score of the test is 30, with a score of 26 or higher considered to be normal. This test, which is executed within 10 minutes, includes different domains: short term memory (5 points); executive function, including Trail Making Test B (TMB), Clock Drawing Test (CDT), and visuospatial function test (cube copying) (5 points); attention and working memory (6 points); language, including naming, repetition, and fluency (6 points); abstraction (similarity) (2 points); and orientation to time and place (6 points). Patients with scores of 26 or higher did not have any cognitive impairments (normal MoCA), whereas patients with scores lower than 26 probably had cognitive impairments.

Depression questionnaire

The Geriatric Depression Scale (GDS) was used to assess depression in the participants. In this questionnaire, all questions are of similar weight and have a yes/no response format. The maximum score of GDS is 15, and the minimum score is zero, with higher scores indicating more severe depression. This scale is one of the best tools for measuring depression in the elderly and patients with dementia. Sensitivity of 92% and specificity of 89% have been reported for this questionnaire (25). The validity and reliability of 15-item GDS were measured by Malekouti et al. in Iran, and the best cut-off point was eight, with 90% sensitivity and 84% specificity (24).

The 15-item GDS captures depressive symptoms over the past week, using a yes/no response format. For ten items, a positive response ('yes') is given a score of one, and for five items, a negative response ('no') is given a score of zero. Also, five items are reverse-scored (one for 'no' and zero for 'yes'). The total score of the items ranges from 0 to 15, with higher scores indicating more depressive symptoms. The GDS-15 score has been used as both continuous and categorical variables elsewhere. We used a cut-off score of ≥ 5 to indicate the presence of clinical depression symptoms (0, GDS-15 score < 5 and 1, GDS-15 score ≥ 5). We also considered the continuous score of GDS-15 as the outcome (26–28).

Anthropometric indices

Body composition indices, including height (stadiometer, Seca 213, Germany), body mass (digital weighing scales, Seca 769, Germany), body mass index (BMI) (kg/m^2), and body fat percentage (BF %) (InBody S10, Biospace Co.Ltd, Seoul, Korea), were assessed in this study.

Maximum strength

The maximum strengths of knee extensions, preacher curls, and handgrips were measured for all participants. One-repetition maximum (1-RM) for leg extensions and preacher curls was also determined,

based on the procedures described by Sheppard and Triplett (29). The participants performed a general warm-up, consisting of five-minute pedaling on a stationary bicycle (50–70 rotations per minute at a resistance level of 1–5), followed by a specific warm-up of two sets (5–20 repetitions at 40–50% of perceived maximal effort). Next, they made 3–5 attempts to reach 1RM, with 3–5 minutes of rest between attempts.

For knee extensions, the participants were asked to sit on a machine (Impulse IT95 Leg Extension, Impulse Health Tech Co. Ltd., Shandong, China). The researcher adjusted the chair in a way that the subject's legs were placed under the pad, and his/her feet pointed to the pad, while extending the knees. In preacher biceps curls, the participant adjusted the preacher bench, held a dumbbell with fully extended arms, and curled it up to shoulder level. Also, a grip strength dynamometer was used to measure the maximum isometric strength of the hand and forearm muscles. After adjusting the handle of the dynamometer for the subjects, they were asked to hold it in their hands, while keeping the arms at the right angles and the elbows on two sides of the body. Participants pressed the dynamometer with maximum isometric effort, which was maintained for about five seconds (30). The best result of the three trials was recorded for each participant.

Functional tests

The timed up and go (TUG) and chair stand tests were used to measure functional abilities. The TUG test requires the participant to stand up from a chair without the use of arms, walk 2.4 meters, turn, return to the chair, and sit (31). Also, the chair stand test requires the participant seated on a chair to stand up as many times as possible within 30 seconds. The participants were instructed to keep their arms crossed at the wrists and hold them in front of the chest. The examiner counted the number of stands performed correctly within 30 seconds (32). Chair sit and reach (CSR) test requires the participant to sit on the edge of a chair, with one foot flat on the floor and the other leg extended forward with the knee straight and heel on the floor. By placing one hand on top of the other, the subject stretched his/her hands toward the toes by bending at the hip. Next, the distance between the tip of the fingertips and the toes was recorded as a score. If the fingertips reached the toes, the score would be zero; if the fingertips did not touch the toes, the score would be negative; and if the fingertips overlapped, the score would be positive. Overall, two trials were conducted for each participant, and the best distance was recorded (31). The Six-minute walk test (6MWT) was designed to assess aerobic fitness. In this test, the participants walked at a self-selected pace and were allowed to stop or change their pace (32). In the indoor setting, two cones were placed 30 meters apart, and the participants were asked to walk back and forth. The walking path was marked every one meter to determine the distance accurately. For safety, a supervisor accompanied the participants.

Brain waves

Electroencephalography (EEG) (SOMNO medics, SSP full EEG, Germany) was used to evaluate the brain waves with high sensitivity. The information related to beta, theta, and alpha changes on EEG test, investigated by a neurologist, was used to determine the patient's status. EEG was obtained over ten

minutes, and then, the percentage of each brain wave and the brain wave index were extracted, based on the visual scale. We also divided theta power by alpha power to calculate the theta/alpha ratio.

Training protocol

The participants in the experimental group performed 24 workouts twice a week for 12 weeks. Each session lasted about 40–60 minutes, including ten minutes of warm-up, 20–40 minutes of main exercises, and ten minutes of cool down. The participants adhered to a combined protocol, including simple brain activities (eyes-closed training and cognitive activities) and physical activities (muscle endurance, balance, and aerobic capacity). The main training protocol consisted of five parts.

The first part of the training protocol included sitting and standing on an armchair, accompanied by shoulder girdle strengthening (three sets with 5–15 reps, followed by a gradual increase in resistance and repetition, using dumbbells and TheraBand). The second part included crossing over five sponge obstacles (height: 15–20 cm) with eyes closed (two repetitions in the first three sessions, gradually increasing to two reps every three sessions); the distance between the obstacles was variable. In the third part, the participants crossed over a safe balance beam board (2 m) with eyes closed (two repetitions in the first three sessions, gradually increasing to two reps every three sessions).

In the fourth part, six-vowel stations were placed in a semicircular arrangement at a four-meter distance in front of the subject with eyes closed. The subjects were asked to identify the sound of each station, move toward it, perform the predetermined exercises for 15 seconds (e.g., butterfly curls, Hercules curls, knee raises, hand raises, and biceps curls), and return. There were only two stations in the first session, which increased by one station every three sessions to reach a total of six stations. In the last part, there were four colored lights in front of the participants, each indicating a predetermined exercise. As long as the light was on (10–15 seconds), the subject was required to perform the relevant exercise (e.g., red light: side-right lunge; blue light: side-left lunge; green light: backward right lunge; and yellow light: backward left lunge). This part lasted for two minutes in the first session, which increased by one minute every three sessions to reach five minutes by the end.

The exercises changed every three sessions and became more intense. The workouts were performed individually, and each individual attended the center at a certain time. The researcher accompanied the participants throughout training. The intensity of training was difficult due to the variety of exercises. To monitor the workout intensity, heart rate (HR) was monitored by a smart watch.

Statistical Methods

Data presented in mean \pm standard deviation (SD). The Statistical Package of Social Sciences (SPSS, IBM, v19) was used to analysis data. A repeated measure analysis of variance ANOVA with the time (T1 vs T2) and protocol (TG vs CG) was performed to analysis data. To assess the magnitude and direction of the linear correlations between percentage change of the performance parameters and perceptual indices (MoCA & GDS), bivariate Pearson's correlation coefficient (r) was calculated. Effect size (ES) was also computed as the change score divided by the SD of the change score to examine the magnitude of

differences while controlling for the influence of the sample size (33) with 0.2 considered as a small ES, 0.5 as a moderate ES and > 0.8 as a large ES (34). The significance level was set at $p \leq 0.05$ for all statistical analyses. To determine the test-retest absolute and relative reliability, the coefficient of variation (CV) and intra-class correlation coefficient (ICC) was calculated. The ICC was calculated by a two-way single measure absolute agreement model and the CV was calculated by formula ($CV = [SD/mean] \times 100$). The CV for tests was < 4.0% and ICC was > 0.98.

Results

The statistical analysis indicated there was a significant main time ($F_{1,12}=13.5$ $p = 0.003$, $\eta p^2:0.53$), group ($F_{1,12}=28.1$ $p = 0.001$, $\eta p^2:0.70$) and interaction effect ($F_{1,12}=40.5$ $p = 0.001$, $\eta p^2: 0.77$) for MoCA. In details, we observed a significant main time ($F_{1,12}=7.9$ $p = 0.016$, $\eta p^2:0.40$), group ($F_{1,12}=5.0$ $p = 0.044$, $\eta p^2:0.30$) and interaction effect ($F_{1,12}=13.6$ $p = 0.003$, $\eta p^2: 0.53$) for attention and working memory. In addition, there were significant differences at short term memory (time: $F_{1,12}=3.2$ $p = 0.101$, $\eta p^2:0.21$), group: $F_{1,12}=12.9$ $p = 0.004$, $\eta p^2:0.52$ and interaction effect: $F_{1,12}=27.0$ $p = 0.001$, $\eta p^2: 0.69$) and executive function and visuospatial power (time: $F_{1,12}=0.1$ $p = 0.991$, $\eta p^2:0.01$), group: $F_{1,12}=22.8$ $p = 0.001$, $\eta p^2:0.66$ and interaction effect: $F_{1,12}=38.8$ $p = 0.001$, $\eta p^2: 0.76$) between groups. However, there were not significant differences between group at orientation (time: $F_{1,12}=0.6$ $p = 0.468$, $\eta p^2:0.05$), group: $F_{1,12}=0.7$ $p = 0.436$, $\eta p^2:0.05$ and interaction effect: $F_{1,12}=2.2$ $p = 0.165$, $\eta p^2: 0.15$), language (time: $F_{1,12}=4.5$ $p = 0.055$, $\eta p^2:0.27$), group: $F_{1,12}=0.23$ $p = 0.636$, $\eta p^2:0.02$ and interaction effect: $F_{1,12}=3.8$ $p = 0.075$, $\eta p^2: 0.24$) and abstraction (time: $F_{1,12}=0.02$ $p = 0.901$, $\eta p^2:0.01$), group: $F_{1,12}=3.3$ $p = 0.096$, $\eta p^2:0.21$ and interaction effect: $F_{1,12}=1.9$ $p = 0.190$, $\eta p^2: 0.14$). For GDS, there was no significant main time ($F_{1,12}=0.2$ $p = 0.631$, $\eta p^2:0.02$), but a significant in group ($F_{1,12}=23.7$ $p = 0.001$, $\eta p^2:0.66$) and interaction effect existed ($F_{1,12}=21.2$ $p = 0.001$, $\eta p^2:0.64$).

Figure 2 near here

Descriptive statistics of performance and perceptual parameters pre- and post-intervention are summarized in Table 1. In overall, TG compare to CG demonstrated substantial improvements in all performance indices following a 12-week intervention. We found a significant main time ($F_{1,12}=6.4$ $p = 0.026$, $\eta p^2:0.35$), group ($F_{1,12}=40.0$ $p = 0.001$, $\eta p^2:0.77$) and interaction effect ($F_{1,12}=53.7$ $p = 0.001$, $\eta p^2:0.82$) for 6 min walking. For chair sit and reach, there was no significant main time ($F_{1,12}=0.9$ $p = 0.342$, $\eta p^2:0.07$), though a significant in group ($F_{1,12}=87.6$ $p = 0.001$, $\eta p^2:0.88$) and interaction effect existed ($F_{1,12}=135.9$ $p = 0.001$, $\eta p^2:0.92$). Furthermore, Following the 12-week intervention, we found a significant main time ($F_{1,12}=11.2$ $p = 0.006$, $\eta p^2:0.48$), group ($F_{1,12}=80.2$ $p = 0.001$, $\eta p^2:0.87$) and interaction effect ($F_{1,12}=61.3$ $p = 0.001$, $\eta p^2:0.84$) for strength of preacher biceps curl. For strength of knee extensions, there also was a significant main time ($F_{1,12}=6.1$ $p = 0.030$, $\eta p^2:0.34$), group ($F_{1,12}=25.1$ $p = 0.001$, $\eta p^2:0.68$) and interaction effect ($F_{1,12}38.8.2$ $p = 0.001$, $\eta p^2:0.76$). For strength of handgrip,

there was no significant main time ($F_{1,12}=2.3$ $p = 0.152$, $\eta p^2:0.16$), but significant in group ($F_{1,12}=63.6$ $p = 0.001$, $\eta p^2:0.84$) and interaction effect ($F_{1,12}=74.2$ $p = 0.001$, $\eta p^2:0.86$).

Table 1
Performance and psychological characteristics of participants pre- and post-intervention

Variable	Group	Pre	Post	% change	Cohen's d	p
6 min walking (m)	TG	177.0 ± 81.5	318.9 ± 85.5	96.9	1.9	0.001
	CG	180.0 ± 66.2	174.2 ± 62.9	-2.6	-0.5	
Knee extension (kg)	TG	10.8 ± 5.6	23.1 ± 10.6	134.6	1.6	0.001
	CG	10.7 ± 4.9	10.0 ± 4.5	-4.5	-0.6	
Biceps curl (kg)	TG	6.4 ± 1.7	10.6 ± 2.5	70.2	2.6	0.001
	CG	6.4 ± 1.6	6.1 ± 1.5	-3.1	-0.3	
Hand grip (kg)	TG	23.1 ± 9.1	31.6 ± 8.9	47.9	2.4	0.001
	CG	22.61 ± 8.3	21.3 ± 8.1	-7.1	-1.4	
30 s stand-up (N)	TG	10.3 ± 3.4	18.5 ± .37	94.8	1.9	0.001
	CG	9.7 ± 3.1	9.2 ± 2.3	-2.7	-0.5	
Timed Up and Go test (s)	TG	11.8 ± 2.5	6.4 ± 1.4	-45.6	-3.5	0.001
	CG	11.8 ± 2.7	12.4 ± 2.9	5.7	0.8	
Chair sit and reach (cm)	TG	18.5 ± 8.1	26.9 ± 7.6	54.5	3.9	0.001
	CG	19.8 ± 8.1	18.7 ± 7.1	-3.7	-0.5	
MoCA	TG	18.6 ± 3.5	23.9 ± 2.3	28.4	1.7	0.001
	CG	19.0 ± 2.1	17.9 ± 2.2	-3.3	-0.5	
GDS	TG	5.4 ± 2.9	2.6 ± 1.9	-49.5	-1.4	0.001
	CG	4.4 ± 2.5	4.5 ± 2.5	6.8	0.2	
Alpha wave (%)	TG	80.0 ± 5.5	83.2 ± 2.7	4.3	0.7	0.002
	CG	78.8 ± 7.7	78.0 ± 7.6	-1.0	-0.6	
Beta wave (%)	TG	3.7 ± 3.1	8.9 ± 3.3	218.3	2.6	0.001
	CG	3.1 ± 1.6	3.0 ± 1.1	5.0	-0.2	
Theta wave (%)	TG	16.2 ± 6.5	7.8 ± 3.7	-51.8	-1.9	0.001
	CG	18.1 ± 6.9	19.0 ± 7.0	5.9	0.6	

TG: Training Group, CG: Control Group; MoCA: The Montreal Cognitive Assessment; GDS: Geriatric Depression Scale

For functional indices, we found a significant main time ($F_{1,12}=12.7$ $p=0.004$, $\eta p^2:0.52$), group ($F_{1,12}=90.9$ $p=0.001$, $\eta p^2:0.88$) and interaction effect ($F_{1,12}=172.1$ $p=0.001$, $\eta p^2:0.94$) for timed up and go test. In addition, there was a significant main time ($F_{1,12}=29.0$ $p=0.001$, $\eta p^2:0.71$), group ($F_{1,12}=54.6$ $p=0.001$, $\eta p^2:0.82$) and interaction effect ($F_{1,12}=41.1$ $p=0.001$, $\eta p^2:0.77$) for chair stand.

Table 1 near here

Figure 3 near here

Following 12 weeks combined training, the percentage of resting average frequency of brain waves in occipital region in the TG increased significantly by 14.5% from, change from alpha range to beta frequency (11.51 Hz to 13.15) Hz, but there was no significant change (-1.4%) in control group (11.13 Hz to 10.95 Hz). Descriptive statistics of the brain waves are presented in Table 1. The results of repeated measure ANOVA showed there were significant main time (within group) ($F_{1,12}=11.4$ $p=0.005$, $\eta p^2:0.48$), group (between group) ($F_{1,12}=63.7$ $p=0.001$, $\eta p^2:0.84$) and interaction (group \times time) effects ($F_{1,12}=39.7$ $p=0.001$, $\eta p^2:0.77$) for resting average frequency of brain waves (Fig. 3). We found no significant main time ($F_{1,12}=3.2$ $p=0.098$, $\eta p^2:0.21$), and group ($F_{1,12}=3.6$ $p=0.080$, $\eta p^2:0.23$) effect, though a significant interaction effect existed ($F_{1,12}=6.7$ $p=0.024$, $\eta p^2:0.36$) for percentage of alpha waves. While for percentage of beta waves, significant main time ($F_{1,12}=19.2$ $p=0.001$, $\eta p^2:0.62$), group ($F_{1,12}=77.2$ $p=0.001$, $\eta p^2:0.86$) and interaction effect ($F_{1,12}=82.1$ $p=0.001$, $\eta p^2:0.87$) were observed. For percentage of theta waves, there were significant main time ($F_{1,12}=14.7$ $p=0.002$, $\eta p^2:0.55$), group ($F_{1,12}=39.5$ $p=0.001$, $\eta p^2:0.77$) and interaction effect ($F_{1,12}=46.2$ $p=0.001$, $\eta p^2:0.79$). There were significant main time ($F_{1,12}=10.5$ $p=0.007$, $\eta p^2:0.47$), group ($F_{1,12}=29.1$ $p=0.001$, $\eta p^2:0.71$) and interaction effect ($F_{1,12}=33.7$ $p=0.001$, $\eta p^2:0.74$) for theta/alpha ratio (Fig. 3).

Table. 2 presents the bivariate Pearson's correlation coefficient (r) between the percentage change of performance parameters and MoCA and GDS. In general, there were moderate to large, positive correlations between MoCA changes and performance induces. Moderate, negative correlations was found between changes in GDS, and performance induces. In addition, MoCA correlated negatively with theta/alpha ratio, while GDS correlated positively.

Table 2 near here

Table 2
The Pearson's correlation coefficient between the variables.

		Hand grip	Knee extension	Biceps curl	30 s stand-up	Timed Up and Go test	6 min walking	Chair sit & reach	theta/alpha ratio
MoCA	r	0.81	0.78	0.63	0.68	-0.68	0.36	0.74	-0.56
	p	0.001	0.001	0.001	0.001	0.001	0.067	0.001	0.003
GDS	r	-0.50	-0.55	-0.61	-0.203	0.56	-0.57	-0.47	0.62
	p	0.010	0.004	0.001	0.319	0.003	0.003	0.016	0.001

The mean (SD) of HR during the intervention period was presented in the Fig. 4. The training begun at 50% of maximal HR and reached to 70% of maximal HR toward the end of intervention. The range of HR were 80 to 125 beat per minute.

Figure 4 near here

Discussion

This study aimed to evaluate the efficacy of a 12-week combined training intervention with visual stimulation on the frequency of brain waves, cognitive status, and physical performance of patients with AD. The results revealed that following the intervention, patients in the TG group experienced significant improvements in cognitive function, particularly short-term memory, attention, working memory, and executive function. We also found significant improvements in the depression status of the TG group, compared to CG.

Moreover, significant improvements were observed in the overall physical performance of the participants. These improvements were associated with the reduction of the theta/alpha ratio, suggesting that the intervention was effective in involving and activating neurons. Also, moderate to relatively strong correlations were observed between cognitive and performance indices. The findings of our study revealed that the combination of exercise training with mental challenges (such as closing the eyes, attending to auditory stimuli, and trying to control balance by relying on proprioceptive receptors) can be used to improve the independence of patients with AD.

Cognitive disorders, including memory, speech, attention, and executive function impairments, are among the characteristics of AD, which can be measured with MoCA test in this population. In our study, after the intervention, cognitive performance (MoCA test) improved with a large effect size (28.4%; $\eta p^2 = 1.7$). Improvements were observed in short-term memory, executive function, attention, and working memory. Also, closing the eyes, as part of our training protocol, activated different brain areas, especially the hippocampus, which are involved in attention, memory, and executive function. Our results are in

agreement with previous research, supporting the protective effects of physical training on cognitive function (35, 36).

Although the exact mechanisms of the protective effect of exercise training on the mental health of AD patients are less clear, several mechanisms have been proposed, including the increase of blood supply to the brain, improvement of metabolic health, production of neurotrophic factors (37), increased size of the hippocampus (12), and increasing gray and white matter volumes in the inferior parietal cortex and the hippocampus over a long period (35, 38). These alterations are associated with memory and cognitive performance, as well as changes in the power of brain waves. In this regard, a previous study showed that even a 12-week period of aerobic training could expedite neuroplasticity and promote brain health in sedentary adults (39); the observed improvements in brain function were attributed to the increased physical activity of the participants.

Depression is one of the most common symptoms and consequences of AD, which exacerbates the negative consequences of this disease. Research has shown that regular exercise training in the short-term had obvious effects on depression management (40). The results of the present study also demonstrated the effectiveness of combined training in reducing depression. Based on the results, depression was inversely correlated with physical fitness indices and positively correlated with the theta/alpha ratio. Several mechanisms can justify the positive effects of exercise on depression. Improvement of independence, daily life activities, and mood is among the advantages of exercise training for reducing depression.

Moreover, exercise-mediated production of neurotransmitters, such as dopamine, serotonin (41), and brain-derived neurotrophic factor (42), contributes to the treatment of depression. Also, AD-induced high cortisol levels exert neurotoxic effects on the hippocampus and promote oxidative stress, leading to depression, neurodegeneration, and cognitive decline (43). On the other hand, one of the protective effects of regular exercise is lowering the serum cortisol level (44). Although these factors were not measured in this study, the observed improvements can be explained by these mechanisms.

The resting alpha and beta waves indicate relaxed and alert wakefulness, and the theta/alpha ratio is indicative of cognitive deficits. Decreased alpha wave power has been reported in AD (4, 5), which is associated with an increase in the theta/alpha ratio. Therefore, the reduction of theta/alpha ratio in our study suggests that a combined training period with mental challenges for AD patients activates the mechanisms in the brain, which improve cognitive processing. This finding is in line with a previous study, which showed that ten weeks of limb exercise significantly increase the alpha and beta wave power in all brain areas of older adults with MCI (45); however, this study did not report the theta/alpha ratio.

Although the exact mechanisms of change in the brain wave ratio due to exercise training are unknown in AD, the alpha wave power seems to be correlated with higher cerebral blood flow in the brain areas, involved in attentional modulation (46). Alpha waves are generated mainly in the occipital and parietal lobes, as well as thalamocortical feedback loops, whereas beta waves mainly originate from the frontal

and temporal lobes (47). The eye-closing part of our training protocol forced the individuals to focus on the auditory and proprioceptive data, originating from beta and alpha waves.

Moreover, the sensory data are distributed in different areas of the cortex through the thalamus. Therefore, our intervention was highly effective in activating the brain parts involved in attention. In contrast, Gutmann et al. (2015) were reported no changes in alpha wave power after four weeks of moderate exercise training (14). It seems that methodological differences can explain these contradicting results. The subjects of the latter study were healthy young men, while the populations of our study were older AD adults. Overall, the findings demonstrated that 12 weeks of training combined with mental challenge reduced the theta/alpha ratio by improving the neurophysiological mechanisms.

AD is associated with the loss of muscle mass and strength, reduced balance, and reduced cardiovascular fitness, leading to inability to perform daily activities, loss of independence, and poor quality of life (1, 3, 48); therefore, our subjects' baseline fitness level was very poor. Our findings showed that three months of combined training caused substantial improvements in the performance indices. Resistance exercises (dumbbells, TheraBand, and rubbers) led to increased strength and maintenance of muscle mass, balance exercises (walking on a beam board) and eyes-closed exercises improved proprioception, and consecutive exercises led to increased cardiovascular fitness.

Improved balance in the present study is especially important, as balance and mobility impairments in AD patients are associated with the risk of falling and reduced quality of life. It is worth mentioning that the observed improvements after exercise training are not population-specific, as comparable increments have been observed in the physical capacity of other populations after a short-term training program (49). Improved fitness components appear to be correlated with the ability to perform daily tasks and quality of life. This finding is in line with a previous study, which examined the effects of exercise training on functional capacity in AD patients (48).

Santana-Sosaet et al. (2008) demonstrated that a 12-week combined training program led to significant improvements in the upper and lower body muscle strength, endurance fitness, balance, and ability to perform daily activities (48). Also, moderate-to-large positive interactions were observed between changes in physical parameters and cognitive function. Moreover, there was a strong association between the change of muscle strength (especially handgrip) and MoCA. This finding was supported by a previous study, which showed a strong relationship between muscle atrophy and declined cognitive function (3). Kim et al. (2019) also reported a positive relationship between the handgrip strength and cognitive function of elderly Korean adults (50). Moreover, Burnes et al. (2008) reported that increased cardiorespiratory fitness is associated with reduced brain atrophy in AD patients (35). Based on the findings, exercise training can be an important adjunct to the pharmacological treatment of AD.

Limitations

We acknowledge that there are some limitations in this study. First, the posttest date coincided with the pandemic of COVID-19 in Iran, and we lost some of our participants. Second, due to the lack of full-time

caregivers, transportation was difficult, and the workout time was not consistent; however, all participants completed 24 workout sessions. Third, we did not have access to quantitative EEG; therefore, we suggest using structural and functional brain imaging to assess quantitative changes in the brain structure and function in the future. Finally, we did not determine the period of time when these adaptations remained constant, which indicates the importance of follow-up after three, six, or even 12 months.

Conclusions

In conclusion, a 12-week combined training program, including resistance, balance, and cardiovascular exercises with closed-eyes stimulation, improved the performance capacity of patients with AD. Also, this intervention improved the brain health and activated neurophysiological mechanisms, which are associated with increased cognitive function and decreased theta/alpha ratio. Moreover, our findings supported the hypothesis that cognitive functions are correlated with muscle strength-related physical fitness in patients with AD.

Abbreviations

1-RM; One-repetition maximum, 6MWT; Six-minute walk test, AD; Alzheimer's disease, ANOVA; Analysis of variance, BF; Body fat, BMI; Body mass index, CDT; Clock Drawing Test, CG; Control group, CSR; Chair sit and reach, CV; Coefficient of variation, EEG; Electroencephalography, ES; Effect size, GDS; Geriatric Depression Scale, HR; Heart rate, IC; Internal consistency, ICC; Intra-class correlation coefficient, MCI; Mild cognitive impairments, MoCA; Montreal Cognitive Assessment, SD; Standard deviation, TG; Training group, TMB; Trail Making Test B, TUG; Timed up and go.

Declarations

Ethics approval and consent to participate

All research procedures were approved by the Ethic committees for Sport Sciences Research Institute of Iran (approval number: IR.SSRI.REC.1398.037) and were conducted in accordance with the Declaration of Helsinki. We obtained written informed consent from participants.

Consent for publication

Consent for publication is not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

SA-S and EP conceived the study. EP, FM and BT conducted the experiments. SA-S and MB analyzed the study. SA-S, FM, and MB interpreted the data for the study. All authors made substantial contributions to the design of the work, drafted the work or revised it critically for important intellectual content, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript

Acknowledgement

The authors would like to acknowledge the memory clinic and sport setting of Roozbeh Hospital, and as well as the patients and caregivers who collaborated us.

References

1. Lane CA, Hardy J, Schott JM. Alzheimer's disease. *Eur J Neurol*. 2018;25(1):59–70. <https://doi.org/10.1111/ene.13439>.
2. McGough EL, Lin SY, Belza B, Becofsky KM, Jones DL, Liu M, et al. A Scoping Review of Physical Performance Outcome Measures Used in Exercise Interventions for Older Adults With Alzheimer Disease and Related Dementias. *J Geriatr Phys Ther*. 2017;42(4):28–74. <https://doi.org/10.1519/JPT.0000000000000159>.
3. Burns JM, Johnson DK, Watts A, Swerdlow RH, Brooks WM. Reduced lean mass in early Alzheimer disease and its association with brain atrophy. *Arch Neurol*. 2010;67(4):428–33. <https://doi.org/10.1001/archneurol.2010.38>.
4. Koelewijn L, Bompas A, Tales A, Brookes MJ, Muthukumaraswamy SD, Bayer A, et al. Alzheimer's disease disrupts alpha and beta-band resting-state oscillatory network connectivity. *Clin Neurophysiol*. 2017;128(11):2347–57. <https://doi.org/10.1016/j.clinph.2017.04.018>.
5. Hsiao F-J, Wang Y-J, Yan S-H, Chen W-T, Lin Y-Y. Altered oscillation and synchronization of default-mode network activity in mild Alzheimer's disease compared to mild cognitive impairment: an electrophysiological study. *PloS One*. 2013;8(7):e68792. <https://doi.org/10.1371/journal.pone.0068792>.
6. Moretti DV, Babiloni C, Binetti G, Cassetta E, Dal Forno G, Ferreric F, et al. Individual analysis of EEG frequency and band power in mild Alzheimer's disease. *Clin Neurophysiol*. 2004;115(2):299–308.

[https://doi.org/10.1016/s1388-2457\(03\)00345-6](https://doi.org/10.1016/s1388-2457(03)00345-6).

7. Lizio R, Vecchio F, Frisoni GB, Ferri R, Rodriguez G, Babiloni C. Electroencephalographic rhythms in Alzheimer's disease. *Int J Alzheimers Dis*. 2011;2011(927573).
<https://doi.org/10.4061/2011/927573>.
8. Babiloni C, Del Percio C, Boccardi M, Lizio R, Lopez S, Carducci F, et al. Occipital sources of resting-state alpha rhythms are related to local gray matter density in subjects with amnesic mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging*. 2015;36(2):556–70.
<https://doi.org/10.1016/j.neurobiolaging.2014.09.011>.
9. Fahimi G, Tabatabaei SM, Fahimi E, Rajebi H. Index of Theta/Alpha Ratio of the Quantitative Electroencephalogram in Alzheimer's Disease: A Case-Control Study. *Acta Med Iran*. 2017;55(8):502–6.
10. Rao AK, Chou A, Bursley B, Smulofsky J, Jezequel J. Systematic review of the effects of exercise on activities of daily living in people with Alzheimer's disease. *Am J Occup Ther*. 2014;68(1):50–6.
<https://doi.org/10.5014/ajot.2014.009035>.
11. Jia RX, Liang JH, Xu Y, Wang YQ. Effects of physical activity and exercise on the cognitive function of patients with Alzheimer disease: a meta-analysis. *BMC Geriatr*. 2019;19(1):181.
<https://doi.org/10.1186/s12877-019-1175-2>.
12. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011;108(7):3017–22.
<https://doi.org/10.1073/pnas.1015950108>.
13. Liu PZ, Nusslock R. Exercise-Mediated Neurogenesis in the Hippocampus via BDNF. *Front Neurosci*. 2018;12:52. <https://doi.org/10.3389/fnins.2018.00052>.
14. Gutmann B, Mierau A, Hulsdunker T, Hildebrand C, Przyklenk A, Hollmann W, et al. Effects of physical exercise on individual resting state EEG alpha peak frequency. *Neural Plast*. 2015;2015:717312.
<https://doi.org/10.1155/2015/717312>.
15. Moraes H, Ferreira C, Deslandes A, Cagy M, Pompeu F, Ribeiro P, et al. Beta and alpha electroencephalographic activity changes after acute exercise. *Arq Neuropsiquiatr*. 2007;65(3A):637–41. <https://doi.org/10.1590/s0004-282x2007000400018>.
16. Hubner L, Godde B, Voelcker-Rehage C. Acute Exercise as an Intervention to Trigger Motor Performance and EEG Beta Activity in Older Adults. *Neural Plast*. 2018;2018:4756785.
<https://doi.org/10.1155/2018/4756785>.
17. Techayasukcharoen R, Iida S, Aoki C. Observing brain function via functional near-infrared spectroscopy during cognitive program training (dual task) in young people. *J Phys Ther Sci*. 2019;31(7):550–5. <https://doi.org/10.1589/jpts.31.550>.
18. Brustio PR, Rabaglietti E, Formica S, Liubicich ME. Dual-task training in older adults: The effect of additional motor tasks on mobility performance. *Arch Gerontol Geriatr*. 2018;75:119–24.
<https://doi.org/10.1016/j.archger.2017.12.003>.

19. Hutt K, Redding E. The effect of an eyes-closed dance-specific training program on dynamic balance in elite pre-professional ballet dancers: a randomized controlled pilot study. *J Dance Med Sci*. 2014;18(1):3–11. <https://doi.org/10.12678/1089-313X.18.1.3>.
20. Lerner Y, Papo D, Zhdanov A, Belozersky L, Hendler T. Eyes wide shut: amygdala mediates eyes-closed effect on emotional experience with music. *PLoS One*. 2009;4(7):e6230. <https://doi.org/10.1371/journal.pone.0006230>.
21. Marx E, Deutschländer A, Stephan T, Dieterich M, Wiesmann M, Brandt T. Eyes open and eyes closed as rest conditions: impact on brain activation patterns. *Neuroimage*. 2004;21(4):1818–24. <https://doi.org/10.1016/j.neuroimage.2003.12.026>.
22. Kan DPX, Croarkin PE, Phang CK, Lee PF. EEG Differences Between Eyes-Closed and Eyes-Open Conditions at the Resting Stage for Euthymic Participants. *Neurophysiology*. 2017;49(6):432–40. <https://doi.org/10.1007/s11062-018-9706-6>.
23. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39(2):175–91. <https://doi.org/10.3758/bf03193146>.
24. Sikaroodi H, Majidi A, Samadi S, Shirzad H, Aghdam H, Azimi Kia A, et al. Evaluating reliability of the montreal cognitive assessment test and its agreement with neurologist diagnosed among patients with cognitive complaints. *Police Medicine*. 2012;1(1):11–7.
25. Bakhtiyari F, Foroughan M, Fakhrzadeh H, Nazari N, Najafi B, Alizadeh M, et al. Validation of the persian version of Abbreviated Mental Test (AMT) in elderly residents of Kahrizak charity foundation. *Iranian Journal of Diabetes Metabolism*. 2014;13(6):487–94.
26. Koohsari MJ, McCormack GR, Nakaya T, Shibata A, Ishii K, Yasunaga A, et al. Urban design and Japanese older adults' depressive symptoms. *Cities*. 2019;87:166–73. <https://doi.org/10.1016/j.cities.2018.09.020>.
27. Cron D, Friedman J, Winder G, Thelen A, Derck J, Fakhoury J, et al. Depression and frailty in patients with end-stage liver disease referred for transplant evaluation. *Am J Transplant*. 2016;16(6):1805–11. <https://doi.org/10.1111/ajt.13639>.
28. Honjo K, Tani Y, Saito M, Sasaki Y, Kondo K, Kawachi I, et al. Living alone or with others and depressive symptoms, and effect modification by residential social cohesion among older adults in Japan: the JAGES longitudinal study. *J Epidemiol*. 2018;28(7):315–22. <https://doi.org/10.2188/jea.JE20170065>.
29. Sheppard J, Triplett N. Program design for resistance training. *Essentials of Strength Training and Conditioning*. 4th ed. Champaign: Human Kinetics; 2016.
30. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing*. 2011;40(4):423–9. <https://doi.org/10.1093/ageing/afr051>.
31. Bigdeli S, Dehghaniyan MH, Amani-Shalamzari S, Rajabi H, Gahreman DE. Functional training with blood occlusion influences muscle quality indices in older adults. *Arch Gerontol Geriatr*.

- 2020;90:104110. <https://doi.org/https://doi.org/10.1016/j.archger.2020.104110>.
32. Rikli RE, Jones CJ. Senior fitness test manual. 2nd ed. Champaign: Human kinetics; 2013.
 33. Dankel SJ, Loenneke JP. Effect Sizes for Paired Data Should Use the Change Score Variability Rather Than the Pre-test Variability. *J Strength Cond Res*. 2018;InPress. <https://doi.org/10.1519/jsc.0000000000002946>.
 34. Batterham AM, Hopkins WG. Making meaningful inferences about magnitudes. *Int J Sports Physiol Perform*. 2006;1(1):50 – 7. <https://doi.org/10.1123/ijsp.1.1.50>.
 35. Burns JM, Cronk BB, Anderson HS, Donnelly JE, Thomas GP, Harsha A, et al. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. *Neurology*. 2008;71(3):210–6. <https://doi.org/10.1212/01.wnl.0000317094.86209.cb>.
 36. Morris JK, Vidoni ED, Johnson DK, Van Sciver A, Mahnken JD, Honea RA, et al. Aerobic exercise for Alzheimer's disease: A randomized controlled pilot trial. *PLoS One*. 2017;12(2):e0170547. <https://doi.org/10.1371/journal.pone.0170547>.
 37. Gallaway PJ, Miyake H, Buchowski MS, Shimada M, Yoshitake Y, Kim AS, et al. Physical activity: a viable way to reduce the risks of mild cognitive impairment, Alzheimer's disease, and vascular dementia in older adults. *Brain Sci*. 2017;7(2):22. <https://doi.org/10.3390/brainsci7020022>.
 38. Voss MW, Heo S, Prakash RS, Erickson KI, Alves H, Chaddock L, et al. The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: results of a one-year exercise intervention. *Hum Brain Mapp*. 2013;34(11):2972–85. <https://doi.org/10.1002/hbm.22119>.
 39. Chapman SB, Aslan S, Spence JS, Defina LF, Keebler MW, Didehbani N, et al. Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging. *Front Aging Neurosci*. 2013;5:75. <https://doi.org/10.3389/fnagi.2013.00075>.
 40. Craft LL, Perna FM. The Benefits of Exercise for the Clinically Depressed. *Prim Care Companion J Clin Psychiatry*. 2004;6(3):104–11. <https://doi.org/10.4088/pcc.v06n0301>.
 41. Paillard T, Rolland Y, de Souto Barreto P. Protective Effects of Physical Exercise in Alzheimer's Disease and Parkinson's Disease: A Narrative Review. *J Clin Neurol*. 2015;11(3):212–9. <https://doi.org/10.3988/jcn.2015.11.3.212>.
 42. Wang R, Holsinger RMD. Exercise-induced brain-derived neurotrophic factor expression: Therapeutic implications for Alzheimer's dementia. *Ageing Res Rev*. 2018;48:109–21. <https://doi.org/10.1016/j.arr.2018.10.002>.
 43. Ouanes S, Popp J. High Cortisol and the Risk of Dementia and Alzheimer's Disease: A Review of the Literature. *Front Aging Neurosci*. 2019;11:43. <https://doi.org/10.3389/fnagi.2019.00043>.
 44. Corazza DI, Sebastião É, Pedroso RV, Andreatto CAA, de Melo Coelho FG, Gobbi S, et al. Influence of chronic exercise on serum cortisol levels in older adults. *Eur Rev Aging Phys Act*. 2014;11:25–34. <https://doi.org/10.1007/s11556-013-0126-8>.
 45. Jiang H, Chen S, Wang L, Liu X. An Investigation of Limbs Exercise as a Treatment in Improving the Psychomotor Speed in Older Adults with Mild Cognitive Impairment. *Brain Sci*. 2019;9(10):277. <https://doi.org/10.3390/brainsci9100277>.

46. Jann K, Koenig T, Dierks T, Boesch C, Federspiel A. Association of individual resting state EEG alpha frequency and cerebral blood flow. *Neuroimage*. 2010;51(1):365–72. <https://doi.org/10.1016/j.neuroimage.2010.02.024>.
47. Academic Press
Introduction to EEG-and speech-based emotion recognition
Abhang PA, Gawali BW, Mehrotra SC. Introduction to EEG-and speech-based emotion recognition: Academic Press; 2016.
48. Santana-Sosa E, Barriopedro MI, López-Mojares LM, Pérez M, Lucia A. Exercise training is beneficial for Alzheimer's patients. *Int J Sports Med*. 2008;29(10):845–50. <https://doi.org/10.1055/s-2008-1038432>.
49. de Vreede PL, Samson MM, van Meeteren NL, Duursma SA, Verhaar HJ. Functional-task exercise versus resistance strength exercise to improve daily function in older women: a randomized, controlled trial. *J Am Geriatr Soc*. 2005;53(1):2–10. <https://doi.org/10.1111/j.1532-5415.2005.53003.x>.
50. Kim KH, Park SK, Lee DR, Lee J. The Relationship between Handgrip Strength and Cognitive Function in Elderly Koreans over 8 Years: A Prospective Population-Based Study Using Korean Longitudinal Study of Ageing. *Korean J Fam Med*. 2019;40(1):9–15. <https://doi.org/10.4082/kjfm.17.0074>.

Figures

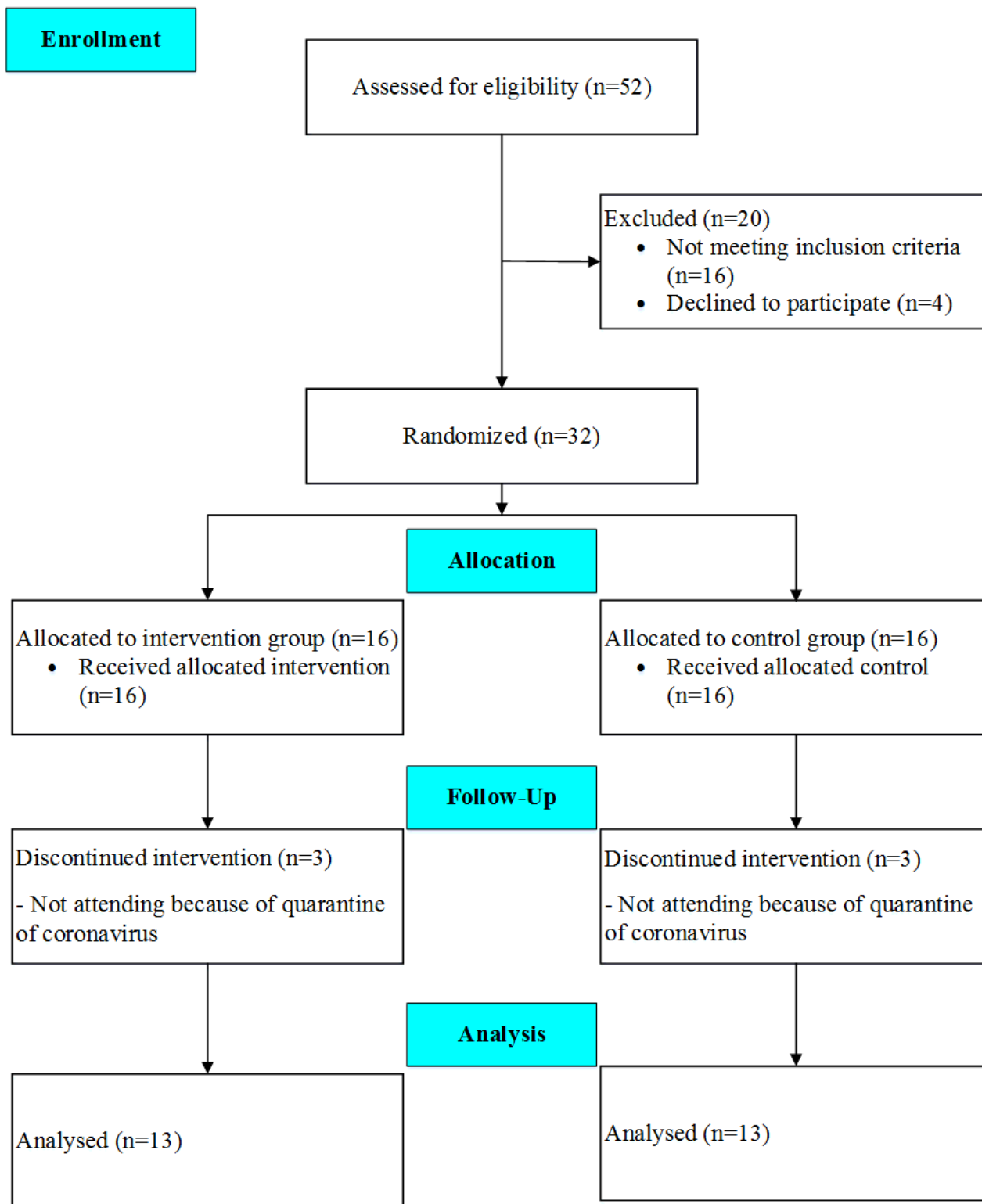


Figure 1

CONSORT Flow diagram of the study.

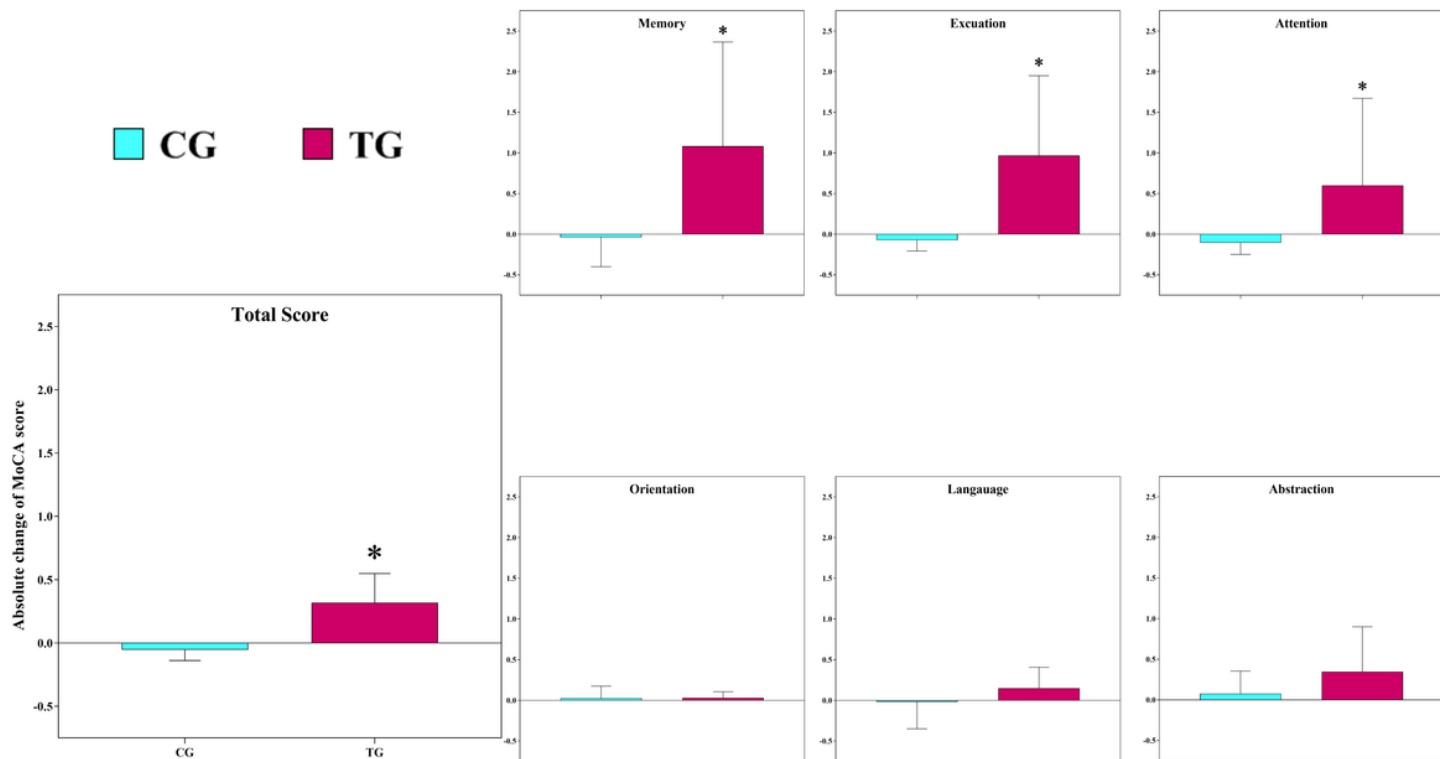


Figure 2

The absolute changes in the scores of the MoCA test following the 12-week intervention in both groups. TG; Training Group, CG; Control Group. *; significant difference between groups.

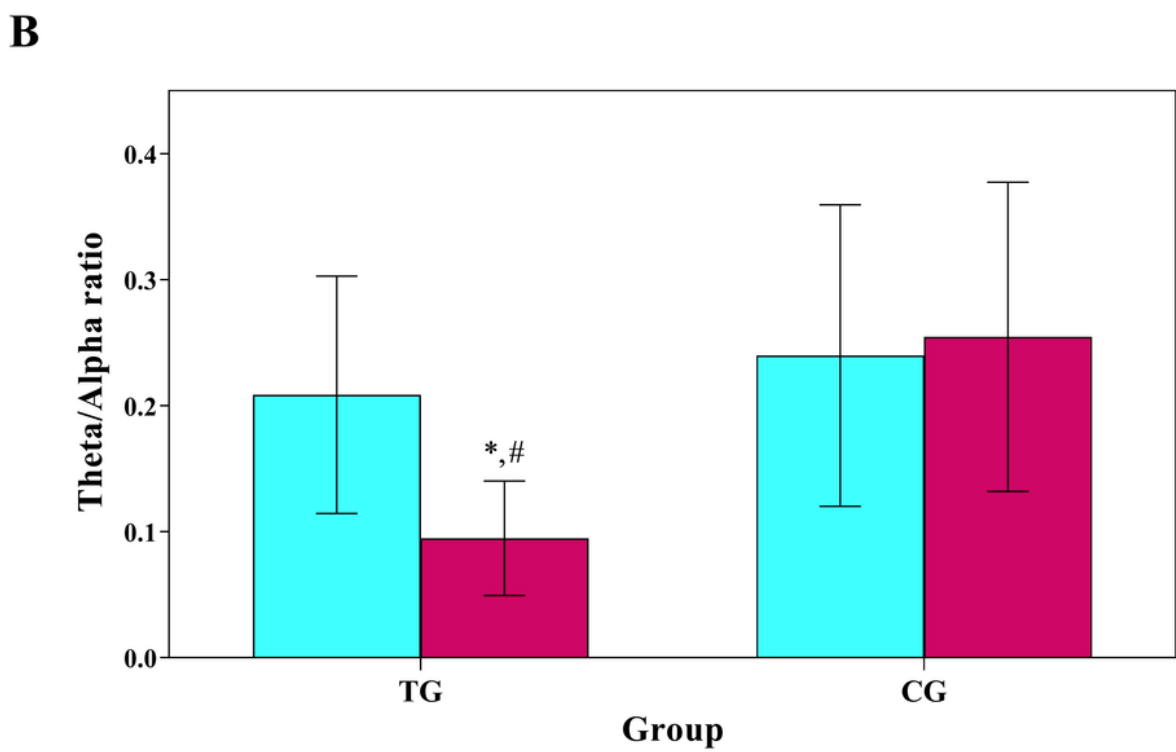
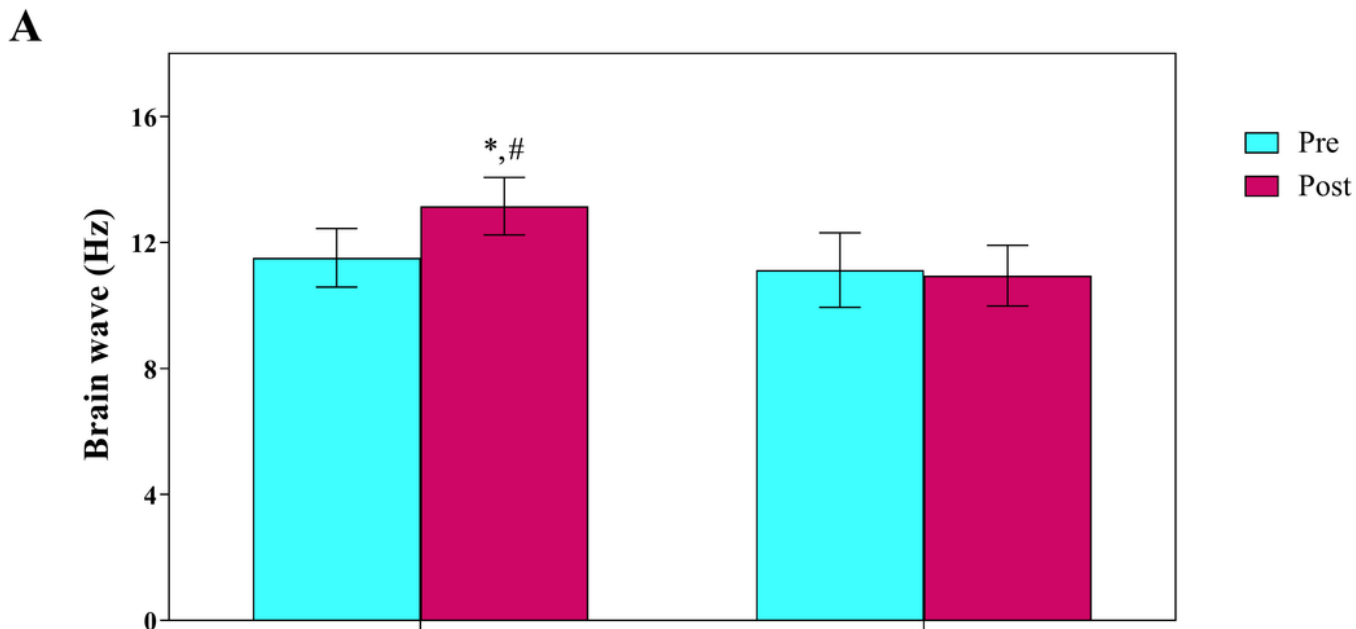


Figure 3

(A) Frequency of brain wave, (B) theta/alpha ratio in 10 min resting EEG. TG; Training Group, CG; Control Group. *, significant difference with pre-test, #; significant difference between groups.

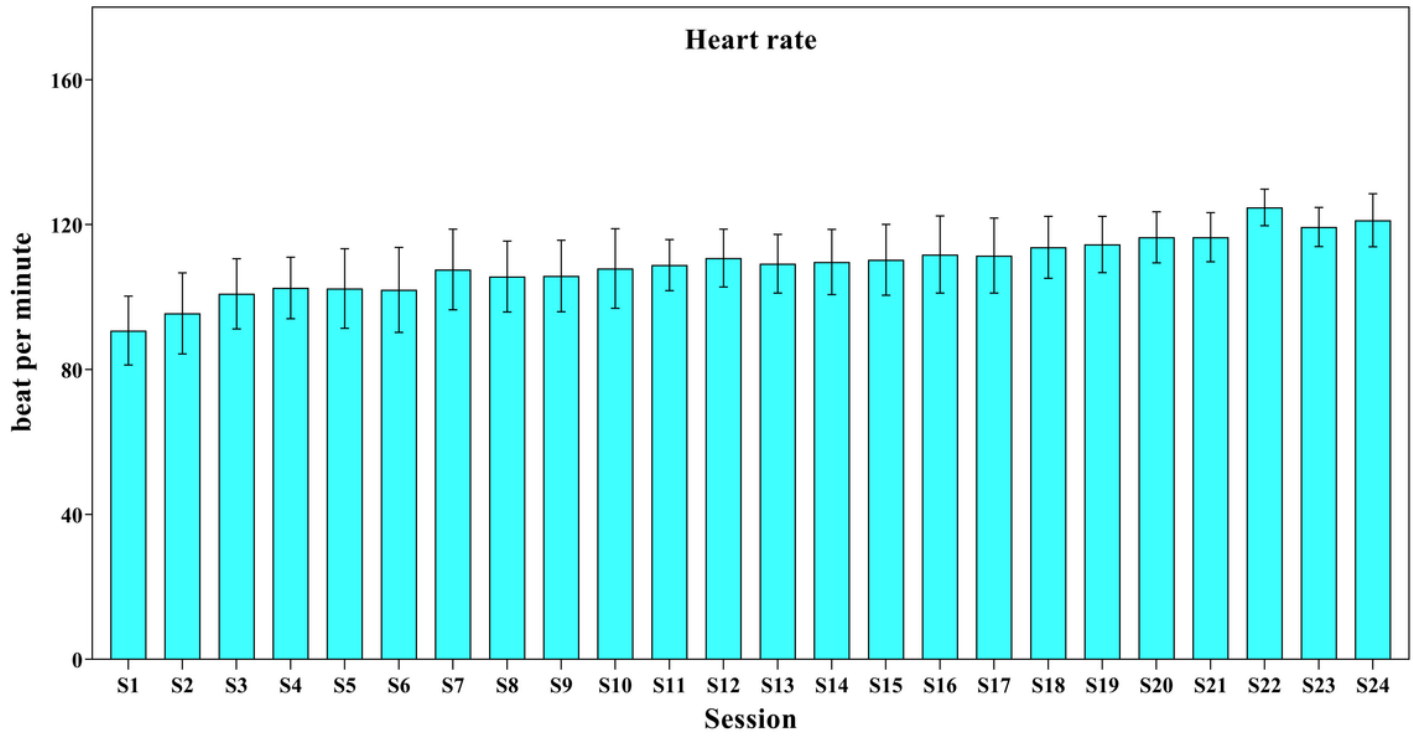


Figure 4

The heart rate (beat/min) during the training sessions.