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Pupillary Responses Reveal Differential Mental Effort After Aerobic, Functional, and Brain Functional Training in Breast Cancer Survivors: A Randomized Crossover Trial

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Abstract

Purpose

Breast cancer survivors (BCS) may report cognitive complaints despite preserved neuropsychological performance, suggesting increased mental effort during executive tasks. This randomized crossover trial compared acute effects of aerobic training (AT), functional training (FT), and Brain Functional Training (BFT) on executive performance and task-evoked pupillary responses in post-treatment BCS.

Methods

16 BCS who had completed primary treatment at least two years before enrollment performed AT, FT, and BFT in randomized order. The trial was registered in ReBEC (RBR-7mf7rrp). Executive performance was assessed with the Stroop Color and Word Test (SCWT) and N-back task with simultaneous pupillary recording. Outcomes were analyzed using mixed models, equivalence tests, GAMM, and integrated curvature.

Results

Behavioral performance did not differ for SCWT reaction time, accuracy, or Stroop effect (all $p \geq 0.508$), or for N-back d' and reaction time (both $p \geq 0.911$). N-back d' decreased with cognitive load ($p < 0.001$). Pupillary trajectories differed for SCWT Δ mm and Δ%, and N-back Δ mm and Δ% (all LRT ≥ 18.849; all $p < 0.001$). AT showed the greatest pupil diameter change. During the SCWT, BFT showed the lowest integrated curvature in Δ mm, 95.8% lower than AT and 98.8% lower than FT, with practically null curvature in Δ%.

Conclusions

The three exercise modalities produced comparable executive performance with distinct pupillary dynamics. BFT sustained inhibitory control with the most stable pupillary trajectory, suggesting lower temporal fluctuation in mental effort.

Implications for Cancer Survivors

BFT may be a promising strategy to reduce the physiological effort required to sustain executive performance in post-treatment BCS.

INTRODUCTION

Breast cancer survivors (BCS) present deficits in executive functions, memory, and processing speed [1, 2]. Neuroimaging evidence has associated these deficits with reduced gray and white matter volume in prefrontal regions [3], as well as changes in the connectivity of brain networks involved in attentional control, including the dorsal attention and default mode networks [4]. Consistently, BCS report that work-related activities, daily routine organization, and family responsibilities require greater mental effort after cancer diagnosis and treatment [5].

In this context, physical exercise has been proposed as a strategy to attenuate cognitive impairments. Recent meta-analyses have identified Aerobic Training (AT) as the most frequently investigated modality and have reported improvements in attention, working memory, executive function, and processing speed in BCS [6, 7]. These effects have been associated with increased cerebral perfusion, greater availability of neurotrophic factors, and modulation of neural networks involved in cognitive control [7–9]. However, it remains unclear whether acute cognitive responses after exercise reflect only systemic adaptations induced by physical effort or whether they are also modulated by task organization during the session.

This issue is relevant because different modalities may impose distinct demands on motor control, attention, and action regulation. Functional Training (FT) [10, 11] organizes exercise through the integration of physical capacities into function-oriented motor tasks, involving multi-joint patterns, postural control, coordination, strength, power, and mobility. Brain Functional Training (BFT) [12, 13], in turn, intentionally manipulates task complexity as a training dose variable, integrating concurrent demands into movement through cognitive-motor and motor-motor tasks. Thus, comparing AT, FT, and BFT allows investigation of whether modalities with different organizational bases produce distinct responses in executive performance and mental effort in BCS.

Assessing these effects, however, remains challenging. Traditionally, they are investigated using neuropsychological tests that provide performance measures, such as accuracy and reaction time to a stimulus [14–16], but these measures may not capture the amount of cognitive resources mobilized to achieve that performance. In BCS, for example, performance in executive tasks may remain similar to that of individuals without a cancer history, despite frontoparietal hyperactivation associated with executive control, suggesting compensatory recruitment of neural resources and greater mental effort during task execution [17–20].

From this perspective, task-evoked pupillary responses (TEPR) have been widely used as a physiological marker of mental effort. Changes in pupil diameter reflect activity of the locus coeruleus–norepinephrine system, which is involved in attention, working memory, and the allocation of attentional resources [21, 22]. Because of its continuous nature and high temporal resolution, pupillometry allows fluctuations in mental effort to be tracked throughout the task, providing information that cannot be obtained solely from behavioral or temporally collapsed measures [22].

Traditionally, TEPR analyses have focused on metrics derived from the temporal curve of the pupillary response, *e.g.*, mean, peak, or maximum dilation amplitude. However, the pupillary response is a dynamic process that evolves continuously over time. For this reason, recent approaches have advocated analyzing the complete temporal trajectory of the pupillary response, allowing differences in the magnitude, duration, temporal stability, changes in slope and temporal pattern of mental effort to be characterized, which may remain hidden in aggregated metrics [22].

To our knowledge, no studies have investigated the acute effects of FT and BFT on executive functioning in BCS, nor examined the temporal dynamics of the pupillary response in this context. Therefore, the present study addresses this gap by comparing FT and BFT with an already established training modality, namely AT, in post-treatment BCS who had completed primary cancer treatment at least two years before enrollment. We hypothesized that BFT, by involving greater task complexity, would result in greater neural efficiency, reflected by lower pupillary dilation, together with preserved performance metrics in neuropsychological tests.

MATERIALS AND METHODS

Study Design and Ethical Aspects

This was a randomized clinical trial of acute effects with a crossover design, structured according to the Consolidated Standards of Reporting Trials (CONSORT) recommendations [23]. Each participant underwent the three experimental conditions: AT, FT, and BFT. The order of the conditions was randomized using a Latin square design, with a minimum interval of 48 hours between sessions. Due to the nature of the interventions, participants and exercise assessors were not blinded to the experimental conditions. However, pupillometry preprocessing and GAMM analyses were performed using coded datasets, so the analyst was blinded to the experimental condition during signal processing and model fitting.

The study was approved by the Research Ethics Committee of the Federal University of Sergipe (approval no. 8.350.704) and registered in the Brazilian Registry of Clinical Trials (ReBEC: RBR-7mf7rrp). All procedures were conducted in accordance with the Declaration of Helsinki and Resolution no. 466/2012 of the Brazilian National Health Council. All participants signed the informed consent form before the start of the procedures.

Participants

The sample consisted of 16 BCS, aged 45 to 65 years, diagnosed with stage I–III breast cancer who had completed primary cancer treatment (surgery, chemotherapy, and/or radiotherapy) at least two years before enrollment. All participants had no active disease or recurrence and, when receiving endocrine therapy, had maintained stable medication for the four months before enrollment and throughout the study.

All participants reported subjective cognitive decline after diagnosis, confirmed by the Cognitive Failures Questionnaire (CFQ; ≥43 points) [24]. Participants had no musculoskeletal disorders, contraindications to physical exercise, or participation in structured physical exercise programs in the previous three months.

Experimental Procedures

The experimental protocol comprised seven laboratory visits. During visit 1, participants signed the informed consent form and underwent anamnesis and clinical, functional, and cognitive characterization assessments. Visits 2 and 3 were dedicated to familiarization with the Stroop Color and Word Test (SCWT) [25] and the N-back task [26], respectively, with five practice rounds to control for learning effects. During visit 4, baseline assessments were performed, including 10 seconds of pupillary recording during visual fixation, the SCWT and N-back task with simultaneous pupillary recording (both tests performed only once), as well as the determination of maximal aerobic speed (MAS) [27].

During visits 5, 6, and 7, participants performed the AT, FT, and BFT sessions in randomized order using a Latin square design. Each experimental visit began with a 10-second baseline pupillary recording, followed by the corresponding exercise session. Immediately after each session, participants performed the SCWT and then the N-back task, both with simultaneous recording of pupil diameter. The experimental flow is presented in Fig. 1.

Assessment Instruments

Cognitive Failures Questionnaire (CFQ)

As an inclusion criterion, the Cognitive Failures Questionnaire (CFQ) was administered. The CFQ is a self-report instrument developed by Broadbent et al. (1982) [28] to assess the frequency of everyday cognitive failures related to perception, memory, and motor control. The instrument consists of 25 items scored on a five-point Likert scale (0 = “never” to 4 = “very often”), with a total score ranging from 0 to 100. Higher scores indicate a greater frequency of perceived cognitive failures. A cutoff score of ≥ 43 points was adopted for participant inclusion, according to Tack et al. (2021) [24].

Functional Assessment of Cancer Therapy-Breast plus Arm Morbidity (FACT-B + 4)

Health-related quality of life was assessed using the Functional Assessment of Cancer Therapy–Breast plus Arm Morbidity (FACT-B + 4), a breast cancer-specific instrument [29, 30]. The questionnaire consists of 40 items distributed across six domains: physical well-being, social/family well-being, emotional well-being, functional well-being, additional concerns related to breast cancer, and upper-limb morbidity. Responses are recorded on a five-point Likert scale ranging from 0 (“not at all”) to 4 (“very much”). After reverse scoring negatively worded items, the total score was calculated, ranging from 0 to 160 points, with higher scores indicating better health-related quality of life [29, 30].

Functional Mobility

Functional mobility was assessed using the Timed Up and Go (TUG) test [31], in its traditional, cognitive, and manual versions. In all conditions, participants began the test seated on a chair with a backrest (45 cm high), with their back supported and feet flat on the floor. At the verbal command “Go,” they stood up from the chair, walked as quickly and safely as possible along a 3-m path, turned around a cone, returned to the chair, and sat down again. Total execution time was recorded in seconds using a digital stopwatch. Three trials were performed, with a 1-min interval between trials, and the shortest time was considered for analysis. Values ≤ 10 s were considered indicative of preserved mobility, as described by Podsiadlo and Richardson (1991) [31, 32].

In the manual dual-task condition (TUG-M) [32], the path was performed while holding a tray (25 cm) with the dominant hand, containing a cup (8 cm in diameter × 9 cm high) filled with water to approximately 1 cm below the rim. The procedure followed that of the traditional TUG, and times ≥ 14.5 s were considered indicative of a higher risk of falls [32].

In the cognitive dual-task condition (TUG-C) [32], participants simultaneously performed a serial subtraction task, starting at 100 and successively subtracting three units throughout the path. The execution procedure followed that of the traditional TUG, and times ≥ 15 s were considered indicative of a higher risk of falls [32].

In addition to absolute execution time, the dual-task cost (DTC) was calculated for the cognitive and manual conditions using the following equation [33]:

$$DTC\,(\%) = \left(\frac{TUG_{DT}\text{-}TUG_{ST}}{TUG_{ST}} \right) \times\ 100$$

where TUG_{DT} corresponds to the time obtained in the dual-task conditions (cognitive or manual), and TUG_{ST} corresponds to the time obtained in the single-task condition. Positive values indicate worse performance during the dual task, reflecting greater cognitive-motor interference on functional mobility [33].

Maximal Aerobic Speed (MAS)

MAS was estimated using the heart rate cost (HRC), according to the method described by Moreno (2007) [27]. Initially, after 15 minutes of rest, resting heart rate (HRrest) was recorded. Participants then performed a 6-minute submaximal stage on a treadmill at an individualized constant speed, adjusted to maintain the rating of perceived exertion between 11 and 13 points on the 6–20 Borg scale [34]. At the end of the stage, the cost speed (Vcost) and the corresponding heart rate (HRcost) were recorded.

Subsequently, a maximal incremental treadmill test was performed with a fixed 1% incline, using increments of 0.5 km·h⁻¹ every 3 minutes until voluntary exhaustion [27]. Heart rate was continuously monitored using a Polar H10 heart rate monitor (Polar Electro Oy, Kempele, Finland), and the highest value recorded during the test was considered the maximal heart rate (HRmax) [27].

MAS was calculated using the equation recommended by Da Silva et al. (2015) [35]:

$$MAS = \frac{HR_{max} - HR_{rest}}{HR_{cost} - HR_{rest}} \times V_{cost}$$

Stroop Color and Word Test (SCWT)

Inhibitory control was assessed using a computerized version of the SCWT, implemented in PsychoPy software (version 2024.2.4), with manual responses using a controller [25]. The protocol consisted of 62 stimuli presented sequentially at the center of the screen, with a fixed interstimulus interval of 500 ms. Of these, 18 were congruent and 44 were incongruent, using the words “yellow,” “blue,” “green,” and “red,” presented in one of the four corresponding colors. Participants were instructed to identify only the ink color, ignoring the semantic content of the word, by pressing the key corresponding to the response. Reaction time (ms) and accuracy (%) were automatically recorded for each trial.

The analyzed variables were mean reaction time for congruent and incongruent stimuli; the Stroop effect, calculated as the difference between mean reaction time in the incongruent and congruent conditions (incongruent RT – congruent RT); and accuracy (%) in both conditions. The Stroop effect was used as an indicator of the cognitive cost associated with inhibitory control.

N-back Task

Working memory and cognitive flexibility were assessed using the N-back task [26], implemented in PsychoPy software (version 2024.2.4). Stimuli consisted of uppercase letters (consonants from the Brazilian Portuguese alphabet) presented sequentially at the center of the screen for 500 ms, followed by a 2500-ms interstimulus interval, during which participants recorded their responses using the keyboard.

The task consisted of four conditions of increasing cognitive load (0-, 1-, 2-, and 3-back), presented in randomized order. In the 0-back condition, participants responded whenever the previously defined target stimulus was presented. In the 1-, 2-, and 3-back conditions, a response was required when the current stimulus matched the one presented one, two, or three positions earlier, respectively. Before each block, specific instructions corresponding to that condition were presented.

The performance variables analyzed were the sensitivity index (d'), calculated based on signal detection theory [36], and mean reaction time (ms) for correct responses in each condition. The d' index was calculated from hit and false

alarm rates, representing a measure of the ability to discriminate target stimuli independently of response bias [36]. The progressive increase in cognitive load across the 0-, 1-, 2-, and 3-back conditions was used to assess working memory performance.

Pupillometry

TEPR, used as a physiological indicator of mental effort, was recorded using the Pupil Core eye-tracking system (Pupil Labs GmbH, Berlin, Germany), composed of two infrared cameras for binocular pupil tracking and one scene camera, with a sampling frequency of 200 Hz [37]. Before each assessment, the system was calibrated using the nine-point calibration procedure available in Pupil Capture software (version 3.5).

Assessments were conducted individually in a quiet, temperature-controlled room (18°C), with constant artificial lighting throughout the experimental session. Participants were instructed to abstain from beverages containing caffeine for 12 hours before the assessment, alcoholic beverages for 24 hours before the assessment, and vigorous physical exercise for 48 hours before the assessment.

Initially, a 10-s baseline period was recorded, during which participants remained seated, looking at a white screen positioned at eye level. Subsequently, pupillary recording was maintained continuously throughout the entire execution of the SCWT and N-back task, allowing simultaneous acquisition of task-evoked pupillary responses during the neuropsychological tests.

Pupil diameter was recorded bilaterally throughout the assessment. For the analyses, the eye with the highest proportion of valid data across the recording was used, reducing the influence of temporary data loss due to blinks or tracking failures. During preprocessing, samples were retained only when the tracking confidence provided by Pupil Labs was ≥ 0.75, according to recommendations for cognitive pupillometry studies [22]. Blinks were removed based on onset and offset events, with the rejection window expanded by 50 ms before blink onset and 150 ms after blink offset [22]. Artifacts and extreme values were removed before reconstruction of the time series [22]. Short internal gaps of up to 500 ms were linearly interpolated, whereas longer gaps were left missing [22]. The signal was then smoothed and baseline-corrected [22].

To make time series with different durations comparable, task time was normalized to relative time from 0 to 100%. Statistical modeling procedures are described in the Statistical Analysis section.

Training Protocols

Aerobic Training (AT)

AT intensity was individualized based on MAS, previously determined according to the protocol described above. The session was performed on a treadmill (Inbramed, Millenium ATL, Brazil) and continuously monitored using a heart rate monitor (Polar H10, Polar Electro, Finland). The protocol began with 5 minutes of walking at 30–40% of MAS, followed by 30 minutes of continuous moderate walking/running at 60–70% of MAS. At the end, a 5-minute cool-down was performed, with gradual speed reduction to light walking at 30–40% of MAS.

Functional Training (FT)

FT was organized into four blocks: movement preparation, neuromuscular 1, neuromuscular 2, and cardiometabolic block. Movement preparation lasted 10 minutes and included mobility exercises for the cervical region, shoulders, hips, knees, and ankles, as well as muscle activation with squats.

The neuromuscular 1 block lasted 12 minutes, with a 1:2 work-to-rest density, consisting of 20 seconds of effort and 40 seconds of rest, performed in two rounds. This block included exercises emphasizing physical capacities such as power, coordination, agility, and speed. The neuromuscular 2 block lasted 12 minutes, with a 1:1 density, consisting of 30 seconds of effort and 30 seconds of rest, also performed in two rounds. This block included strength and muscular endurance exercises involving pulling, squatting, pushing, lifting, and carrying patterns. The cardiometabolic block lasted 4 to 6 minutes, with a 1:2 density, consisting of 10 seconds of effort and 20 seconds of rest, in 10 rounds of interval running. The number of repetitions/rounds performed was recorded in each block to characterize the external volume of the session. The specific exercises included in each block are described in Online Resource 1, Supplementary Chart 1.

Brain Functional Training (BFT)

BFT maintained the same temporal structure and block organization as FT but intentionally manipulated task complexity by integrating concurrent demands into movement. In cognitive-motor tasks, complexity was increased through the simultaneous execution of cognitive tasks with the motor pattern, intentionally recruiting working memory (WM), inhibitory control (IC), and cognitive flexibility (CF). In motor-motor tasks, complexity was increased by adding a second motor demand to the main exercise, increasing the requirements for coordination, postural control, motor adjustment, and action regulation during movement.

The distribution of tasks in BFT was planned to vary both the motor pattern and the predominantly recruited executive function across blocks. Thus, exercises similar to those used in FT were combined with auditory commands, response rules, information updating tasks, sequence memorization, inhibition of automatic responses, alternation of motor patterns, and simultaneous execution of additional movements. The number of repetitions/rounds performed was recorded in each block to characterize the external volume of the session. The specific exercises included in each block are described in Online Resource 1, Supplementary Chart 1.

Statistical Analysis

Behavioral analyses were performed in Jamovi (version 2.7.17), using the GAMLj module for linear mixed models. Pupillary analyses were conducted using generalized additive mixed models (GAMM). A significance level of 5% ($\alpha = 0.05$) was adopted for all analyses.

Initially, sample characteristics were presented as mean ± standard deviation or absolute and relative frequency, according to the nature of the variables. Baseline cognitive assessments were presented descriptively only, as they were not performed immediately before each experimental condition.

For the behavioral variables of the SCWT, linear mixed models (LMM) were fitted with experimental condition (AT, FT, and BFT) as a fixed effect and participant as a random intercept. For the N-back task, LMM were fitted with experimental condition, cognitive load (0-, 1-, 2-, and 3-back), and the condition × load interaction as fixed effects, with participant as a random intercept. When significant effects of interest were identified, pairwise comparisons were performed with adjustment for multiple comparisons.

Potential order effects inherent to the crossover design were examined by adding session order as an additional fixed effect to the behavioral and pupillary models. For behavioral outcomes, potential carryover effects were also examined by adding previous condition as an additional fixed effect. No significant order effects were observed in the behavioral or pupillary models, and no significant carryover effects were observed in the behavioral models; therefore, these terms were not retained in the final models.

Behavioral equivalence across conditions was examined for accuracy (SCWT) and sensitivity (d', N-back) using the two one-sided tests (TOST) procedure [38, 39]. For each pairwise comparison (AT, FT, BFT), equivalence was assessed against two pre-specified smallest effect sizes of interest: a standardized bound of dz = 0.50 and a fixed operational bound (5 percentage points for accuracy and 0.5 units for d'); a comparison was considered equivalent when the 90% confidence interval of the paired difference fell entirely within these bounds. Given the specific clinical population and the randomized crossover design, sample size was determined by feasibility rather than by a formal a priori power calculation. Therefore, a sensitivity power analysis ($\alpha = 0.05$, power = 0.80) was performed to estimate the minimum detectable effect size, rather than observed power, which has limited interpretability in this context [40, 41]. These analyses were conducted in Python using the statsmodels library [42], with the TOST procedure implemented directly as two one-sided tests on the paired differences.

Pupillary signals were preprocessed according to the methodological recommendations of Mathôt and Vilotijević (2023) [22] for cognitive pupillometry studies, including artifact removal, interpolation of short data losses, signal smoothing, baseline correction, and temporal normalization. At each time point, absolute change in pupil diameter was calculated as the difference between the observed pupil diameter and the baseline recorded immediately before the cognitive task: Δ (mm) = pupil diameter − baseline pupil diameter. Percentage change was calculated point by point as Δ (%) = 100 × [(pupil diameter − baseline pupil diameter)/baseline pupil diameter]. Thus, each pupillary time series was normalized using its corresponding baseline before model fitting. Subsequently, pupillary trajectories were analyzed using separate GAMMs for each cognitive task and pupillary metric, Δ (mm) and Δ (%). Participants were included as a grouping variable, accounting for the dependence of intraindividual observations over time.

For each task and pupillary metric, the effect of experimental condition was evaluated using likelihood ratio tests (LRT), comparing models with a common trajectory across conditions and models with condition-specific trajectories for AT, FT, and BFT. When significant differences were identified, pairwise comparisons were performed with Holm adjustment for multiple comparisons.

To quantify the temporal shape of the pupillary trajectories, integrated curvature was calculated from the absolute value of the second derivative of the GAMM-fitted functions across relative task time. Curvature was computed for each condition and pupillary metric within each task. Lower curvature values indicate flatter trajectories, whereas higher values indicate greater changes in slope throughout task execution. Descriptive relative differences between conditions were calculated as [(condition − comparator)/comparator] × 100.

RESULTS

Sample Characterization

The sample consisted of 16 BCS, with a mean age of 55.7 ± 7.0 years. All participants had undergone surgery, chemotherapy, and radiotherapy, with a mean time since diagnosis of 8.1 ± 3.0 years and a mean time since treatment completion of 7.1 ± 3.0 years. Four participants (25.0%) were currently using endocrine therapy with anastrozole. Participants had a mean BMI of 26.8 ± 4.0 kg/m² and MAS of 7.0 ± 0.7 km/h. Mean TUG, TUG-C, and TUG-M times remained below the cutoff points indicative of reduced mobility or higher risk of falls. The mean CFQ score was 54.4 ± 14.5 points, and the mean FACT-B score was 108.1 ± 22.8 points. The remaining sociodemographic, clinical, anthropometric, and functional characteristics are presented in Table 1.

Table 1
Sociodemographic, Clinical, Anthropometric, and Functional Characteristics of the Sample (n = 16)

Variable	Mean ± SD	n (%)
Sociodemographic characteristics		
Age, years	55.7 ± 7.0	-
Education		
Elementary school	-	3 (18.8)
High school	-	8 (50.0)
Higher education	-	5 (31.2)
Clinical characteristics		
Time since diagnosis, years	8.1 ± 3.0	-
Time since treatment completion, years	7.1 ± 3.0	-
Surgery	-	16 (100.0)
Chemotherapy	-	16 (100.0)
Radiotherapy	-	16 (100.0)
Current endocrine therapy	-	4 (25.0)
Anastrozole	-	4 (25.0)
Pain, VAS	3.6 ± 3.1	-
Sleep, h/night	6.5 ± 1.5	-
Perceived fatigue		
Mild	-	10 (62.5)
Moderate	-	6 (37.5)
Anthropometric and functional characteristics		
Body mass, kg	65.6 ± 8.2	-
Height, cm	156.9 ± 7.0	-
BMI, kg/m²	26.8 ± 4.0	-
MAS, km/h	7.0 ± 0.7	-
TUG, s	6.2 ± 0.7	-
TUG-C, s	7.0 ± 1.1	-
TUG-M, s	7.4 ± 0.7	-

Note: Values are presented as mean ± standard deviation or n (%). VAS: visual analog scale; BMI: body mass index; MAS: maximal aerobic speed; TUG: Timed Up and Go; TUG-C: cognitive Timed Up and Go; TUG-M: motor Timed Up and Go; CFQ: Cognitive Failures Questionnaire; FACT-B: Functional Assessment of Cancer Therapy–Breast.

Variable	Mean ± SD	n (%)
Sociodemographic characteristics		
Cognitive dual-task cost, %	12.7 ± 10.2	-
Motor dual-task cost, %	18.9 ± 11.9	-
Questionnaires		
CFQ	54.4 ± 14.5	-
FACT-B	108.1 ± 22.8	-

Note: Values are presented as mean ± standard deviation or n (%). VAS: visual analog scale; BMI: body mass index; MAS: maximal aerobic speed; TUG: Timed Up and Go; TUG-C: cognitive Timed Up and Go; TUG-M: motor Timed Up and Go; CFQ: Cognitive Failures Questionnaire; FACT-B: Functional Assessment of Cancer Therapy–Breast.

External Load of the Experimental Sessions

The external load performed during the experimental sessions is presented in Online Resource 1, Supplementary Table 1. In AT, the load was described by intensity relative to MAS, speed, and estimated distance. In FT and BFT, the load was described by the volume performed in the neuromuscular and cardiometabolic blocks. FT showed a higher total volume performed compared with BFT, as well as higher volume in the Neuro I and Neuro II blocks. There was no difference between FT and BFT for cardiometabolic volume. In BFT, the mean accuracy of tasks with concurrent demands was 77.7 ± 10.9%.

Performance on the Stroop Color and Word Test

Performance on the SCWT is presented in Online Resource 1, Supplementary Table 2. Overall, participants maintained similar performance across the three experimental conditions. Linear mixed models did not indicate a significant effect of condition for reaction time in congruent stimuli, $F(2, 30) = 0.676$; $p = 0.516$, or incongruent stimuli, $F(2, 30) = 0.531$; $p = 0.593$. No significant order or carryover effects were observed for SCWT outcomes (all $p > 0.18$).

No significant effects of condition were observed for accuracy in congruent stimuli, $F(2, 30) = 0.692$; $p = 0.508$, or incongruent stimuli, $F(2, 30) = 0.612$; $p = 0.549$. The Stroop effect, calculated as the difference between incongruent and congruent reaction time, also did not differ among FT, BFT, and AT, $F(2, 30) = 0.141$; $p = 0.869$. These results indicate that the three experimental conditions produced similar behavioral performance in inhibitory control. Equivalence tests confirmed that accuracy (congruent, incongruent, and total) was statistically equivalent across all conditions within the ± 5 percentage-point bound.

Performance on the N-back Task

Performance on the N-back task is presented in Online Resource 1, Supplementary Table 3. Overall, a reduction in discriminative performance was observed as cognitive load increased, regardless of the experimental condition. Linear mixed models were conducted considering only the experimental conditions FT, BFT, and AT, whereas the baseline assessment was presented only descriptively.

For d', the linear mixed model did not indicate a significant effect of experimental condition, $F(2, 165) = 0.09$; $p = 0.911$. However, a significant effect of cognitive load was observed, $F(3, 165) = 109.74$; $p < 0.001$, indicating reduced

performance as task demand increased. The condition × load interaction was not significant, F(6, 165) = 0.60; p = 0.733, suggesting that the effect of cognitive load was similar across FT, BFT, and AT. No significant order or carryover effects were observed for N-back sensitivity outcomes (all $p > 0.13$).

For mean reaction time of correct responses, the linear mixed model did not indicate a significant effect of experimental condition, F(2, 111.30) = 0.01; p = 0.986, cognitive load, F(3, 111.63) = 0.55; p = 0.650, or the condition × load interaction, F(6, 111.02) = 0.21; p = 0.972. These findings indicate that response time for correct responses was similar across experimental conditions and task load levels. No significant order or carryover effects were observed for N-back reaction time outcomes (all $p > 0.67$).

Taken together, the results indicate that the three experimental conditions produced similar behavioral performance in working memory. The variation observed in d' was mainly associated with the increase in task cognitive load, rather than the type of intervention performed. Equivalence tests confirmed that N-back sensitivity (d') was equivalent across conditions at most load levels. A sensitivity power analysis indicated that the design was powered (80%) to detect effects of dz ≈ 0.75 or larger for pairwise contrasts.

Pupillometry Data Quality

Before GAMM fitting, signal yield and preprocessing losses were summarized for the pupillary recordings included in the primary models. For the SCWT, 580,252 of 663,625 recorded samples met the tracking-confidence criterion, corresponding to 87.44% of the acquired data. The mean number of confidence-qualified samples per series was 12,346 ± 4,657, with a mean temporal coverage of 150.19 ± 50.90 s. Artifacts represented 17.22% of the SCWT data, and 15.41% of the recorded samples were reconstructed by linear interpolation.

For the N-back task, 1,937,480 of 2,157,011 recorded samples met the tracking-confidence criterion, corresponding to 89.82% of the acquired data. The mean number of confidence-qualified samples per series was 41,223 ± 7,788, with a mean temporal coverage of 485.55 ± 73.90 s. Artifacts represented 14.88% of the N-back data, and 13.65% of the recorded samples were reconstructed by linear interpolation. One BFT participant-condition series was excluded from the primary pupillary analysis following MAD-based outlier detection. Full signal-yield and preprocessing-quality data are presented in Online Resource 1, Supplementary Table 4.

Pupillary Dynamics During Cognitive Tasks

Pupillary dynamics during the SCWT and N-back task are presented in Fig. 2. Trajectories were analyzed using GAMM, considering the absolute change in pupil diameter relative to the baseline immediately preceding the cognitive test, Δ (mm), and the corresponding percentage change, Δ (%).

The results of the pupillary analysis are presented in Table 2, Part A. Condition-specific trajectories differed significantly for both Δ (mm) and Δ (%). For Δ (mm), pairwise trajectory comparisons indicated significant differences between AT and FT, AT and BFT, and FT and BFT. For Δ (%), pairwise trajectory comparisons also indicated significant differences among the three experimental conditions.

In the N-back task, condition-specific trajectories also differed significantly for both Δ (mm) and Δ (%). For Δ (mm), pairwise trajectory comparisons indicated significant differences between AT and FT and between AT and BFT, whereas FT and BFT did not differ. For Δ (%), significant differences were observed between AT and FT, AT and BFT, and FT and BFT.

Taken together, the GAMM results indicate that the experimental conditions differed in the temporal dynamics of pupil diameter change during both the SCWT and N-back task. The most distinct pattern was observed during the SCWT after BFT, which showed the lowest and most stable pupillary trajectory across task execution.

Table 2
Pupillary trajectory models and integrated curvature

A – GAMM parametric effects and temporal trajectory comparisons

Task	Metric	Global model LRT (*p*)	Comparison	β (SE)	t (*p*)	Pairwise trajectory LRT (*p* Holm)
SCWT	Δ (mm)	31.938 (< 0.001)	FT – AT	−0.349 (0.397)	−0.879 (0.380)	5.504 (0.039)*
			BFT – AT	−0.396 (0.404)	−0.979 (0.328)	27.451 (< 0.001)*
			FT – BFT	0.046 (0.404)	0.115 (0.909)	8.449 (0.039)*
SCWT	Δ (%)	44.329 (< 0.001)	FT – AT	−17.930 (19.656)	−0.912 (0.362)	14.876 (< 0.001)*
			BFT – AT	−22.824 (19.980)	−1.142 (0.253)	34.392 (< 0.001)*
			FT – BFT	4.893 (19.980)	0.245 (0.807)	6.996 (0.039)*
N-back	Δ (mm)	18.849 (< 0.001)	FT – AT	−0.867 (0.383)	−2.265 (0.024)*	12.675 (< 0.001)*
			BFT – AT	−0.677 (0.390)	−1.737 (0.083)	12.218 (< 0.001)*
			FT – BFT	−0.190 (0.390)	−0.587 (0.626)	0.000 (1.000)
N-back	Δ (%)	40.978 (< 0.001)	FT – AT	−72.986 (28.850)	−2.530 (0.011)*	15.116 (< 0.001)*
			BFT – AT	−63.287 (29.334)	−2.157 (0.031)*	32.376 (< 0.001)*
			FT – BFT	−9.699 (29.334)	−0.331 (0.741)	3.089 (0.032)*

B – Integrated curvature of GAMM-fitted pupillary trajectories

Task	Metric	Integrated curvature	Descriptive relative difference, %

Note: Part A presents GAMM parametric coefficients and pairwise trajectory comparisons. Global model LRTs compare models with a common temporal trajectory across conditions against models with condition-specific trajectories. AT was the reference condition for the parametric coefficients. Negative β values indicate lower estimated overall response levels relative to AT. Pairwise trajectory LRTs assess differences in temporal shape; p values were adjusted using Holm's method within each task and metric. Part B presents integrated curvature calculated from the absolute value of the second derivative of the GAMM-fitted trajectories across relative task time. Lower curvature values indicate flatter trajectories, whereas higher values indicate greater changes in slope throughout task execution. Descriptive relative differences were calculated as [(condition − comparator)/comparator] × 100. *$p < 0.05$. β: estimated coefficient; SE: standard error; LRT: likelihood-ratio test; pHolm: Holm-adjusted p value; SCWT: Stroop Color and Word Test; AT: aerobic training; FT: functional training; BFT: Brain Functional Training; GAMM: generalized additive mixed model.

A – GAMM parametric effects and temporal trajectory comparisons							
Task	**Metric**	**Global model LRT (*p*)**	**Comparison**	**β (SE)**	**t (*p*)**	**Pairwise trajectory LRT (*p* Holm)**	
		AT	**FT**	**BFT**	**FT vs AT**	**BFT vs AT**	**BFT vs FT**
SCWT	Δ (mm)	0.00939	0.03167	0.00039	237.3	-95.8	-98.8
SCWT	Δ (%)	0.4934	0.7782	0.0000015	57.7	-100.0	-100.0
N-back	Δ (mm)	0.03203	0.01939	0.01660	-39.5	-48.2	-14.4
N-back	Δ (%)	1.508	0.663	0.822	-56.0	-45.5	24.0

Note: Part A presents GAMM parametric coefficients and pairwise trajectory comparisons. Global model LRTs compare models with a common temporal trajectory across conditions against models with condition-specific trajectories. AT was the reference condition for the parametric coefficients. Negative β values indicate lower estimated overall response levels relative to AT. Pairwise trajectory LRTs assess differences in temporal shape; p values were adjusted using Holm's method within each task and metric. Part B presents integrated curvature calculated from the absolute value of the second derivative of the GAMM-fitted trajectories across relative task time. Lower curvature values indicate flatter trajectories, whereas higher values indicate greater changes in slope throughout task execution. Descriptive relative differences were calculated as [(condition − comparator)/comparator] × 100. *$p < 0.05$. β: estimated coefficient; SE: standard error; LRT: likelihood-ratio test; pHolm: Holm-adjusted p value; SCWT: Stroop Color and Word Test; AT: aerobic training; FT: functional training; BFT: Brain Functional Training; GAMM: generalized additive mixed model.

Temporal Curvature of Pupillary Trajectories

To characterize the temporal shape of the pupillary trajectories, integrated curvature was calculated from the absolute value of the second derivative of the GAMM-fitted functions across relative task time. The integrated curvature results are presented in Table 2, Part B. Lower curvature values indicate flatter trajectories, whereas higher values indicate greater changes in slope throughout task execution.

In the SCWT, BFT showed the lowest curvature in both metrics. For Δ (mm), curvature after BFT was 95.8% lower than after AT and 98.8% lower than after FT. In contrast, FT showed curvature 237.3% higher than AT. For Δ (%), the BFT trajectory was nearly flat, whereas FT showed curvature 57.7% higher than AT.

In the N-back task, AT showed the highest curvature in both metrics. For Δ (mm), curvature was 39.5% lower after FT and 48.2% lower after BFT compared with AT. For Δ (%), curvature was 56.0% lower after FT and 45.5% lower after BFT compared with AT.

Together, these findings indicate that the temporal organization of the pupillary response differed between tasks. The most pronounced pattern was observed during the SCWT, in which BFT produced an almost flat pupillary trajectory, consistent with a stationary response profile during inhibitory control.

DISCUSSION

The present study investigated the acute effects of three exercise modalities, AT, FT, and BFT, on behavioral performance in executive tasks and on changes in pupil diameter in BCS. The three conditions produced similar

performance on the SCWT and N-back task, indicating that none of the modalities detectably modified the final product of cognitive task performance in the immediate post-exercise period. However, the pupillary curves differed between conditions, indicating that equivalent executive performance was sustained by distinct physiological patterns after AT, FT, and BFT. Curvature quantified this temporal difference: whereas some conditions showed greater changes in slope throughout the task, BFT showed a more stable, virtually flat trajectory, especially during the SCWT.

The equivalence in behavioral performance should be interpreted in relation to the functional profile of the sample. Participants showed preserved mobility, with mean TUG, TUG-C, and TUG-M times of 6.2 s, 7.0 s, and 7.4 s, respectively, all below the cutoff points adopted for reduced mobility or increased fall risk [32]. Cognitive and motor dual-task costs were positive, 12.7 ± 10.2% and 18.9 ± 11.9%, indicating measurable cognitive-motor interference when a concurrent demand was added to the simple TUG. However, absolute times remained within the expected range for preserved functional mobility. This profile suggests a sample with detectable dual-task interference but without marked functional impairment, which may have reduced the sensitivity of reaction time, accuracy, and d' to detect additional acute gains after a single exercise session.

This interpretation is particularly relevant in BCS, because cancer-related cognitive impairment does not always manifest as an evident decline in neuropsychological performance [1, 4, 20]. Wefel et al. (2010) [2] described that cognitive deficits after cancer treatment may involve attention, processing speed, working memory, and executive functions, with substantial interindividual variability [2]. Jim et al. (2012) [1] showed that subjective cognitive complaints are not always strongly associated with performance on standardized tests, suggesting that these instruments may not capture the cost required to maintain performance [1].

Neuroimaging studies reinforce this interpretation by demonstrating structural and functional alterations in frontoparietal networks of BCS even when their behavioral performance is preserved, a pattern compatible with compensatory recruitment [4, 18]. In this context, similar performance between conditions does not imply the same mental effort during task execution.

Pupillometry allows this physiological difference to be examined during the task. Since the classic studies by Kahneman and Beatty (1966) [43], pupil dilation has been associated with the mental effort required to process information and sustain attention during cognitive tasks [43]. This interpretation was refined by neurophysiological models linking pupil dynamics to the activity of the locus coeruleus-norepinephrine system, involved in the regulation of arousal, attentional responsiveness, and resource mobilization during the task [44]. Recent reviews reinforce that TEPR tracks variations in cognitive demand, especially in tasks requiring executive control, decision-making, information updating, and conflict resolution [22, 45]. Therefore, when two conditions produce similar performance but different pupillary trajectories, the most parsimonious interpretation is that the same performance was sustained with different levels of mental effort.

In the present study, AT produced the greatest change in pupil diameter during both the SCWT and N-back task. This change occurred without corresponding behavioral improvement, indicating greater physiological mobilization to sustain equivalent performance. This interpretation is consistent with the literature on acute aerobic exercise, which describes transient increases in physiological activation and arousal after exercise, with cognitive effects depending on intensity, timing of assessment, and task type [46, 47]. Thus, AT may have increased the general readiness of the organism without producing a state specifically adjusted to the executive demands of the SCWT or N-back task.

BFT showed the most distinct temporal pattern, especially during the SCWT. In this task, the pupillary trajectory after BFT remained nearly flat, with the lowest integrated curvature in both Δ (mm) and Δ (%). Curvature after BFT was 95.8% lower than after AT and 98.8% lower than after FT on the absolute scale, and was practically null on the percentage scale. This behavior indicates that inhibitory control was sustained with high physiological stability throughout the task, despite behavioral performance comparable to the other conditions. The response after BFT indicated temporal stability during inhibitory control, without progressive accumulation or saturation of pupil change.

This pattern may be related to the fact that BFT already required, during the session itself, integration between movement and executive control. Participants had to respond to commands, inhibit automatic responses, update information, make decisions, and switch rules while performing the exercises [12, 13]. Thus, the post-exercise SCWT recruited processes that had been required only a few minutes earlier. Because this task requires inhibition of an automatic response and interference resolution [48], the low curvature after BFT may indicate more stable allocation of attentional-executive resources from the beginning of the task.

The external load analysis reinforces this interpretation. BFT showed lower total volume than FT (283.6 ± 32.7 vs. 348.8 ± 44.9 repetitions/rounds; $p < 0.001$), as well as lower volume in the Neuro I and Neuro II blocks. Cardiometabolic volume, on the other hand, did not differ between the two modalities. Thus, the more stable pupillary trajectory after BFT does not appear to be associated with a greater physical volume performed. The central difference between sessions was in the organization of the dose: in BFT, part of the motor volume was replaced by concurrent tasks performed with a mean accuracy of 77.7 ± 10.9%. This finding corroborates the interpretation that cognitive-motor complexity, rather than the total number of repetitions, was relevant for modulating the pupillary response during inhibitory control.

This interpretation is supported by pupillometry evidence showing that training can reduce the physiological cost of cognitive execution [49]. Burge et al. (2013) [49] observed that, after processing speed training, participants showed smaller pupil diameter during complex visual tasks, a result interpreted as greater efficiency in the allocation of attentional resources. The protocol involved identification of central and peripheral stimuli, distractors, and progressive reduction in stimulus presentation time [49]. Although the present study evaluated an acute response to exercise, the findings converge in indicating that performance can be maintained with lower pupillary cost when the intervention recruits attentional processes relevant to the subsequent task.

During the SCWT, FT showed the highest temporal curvature of the pupillary trajectory, indicating greater oscillation of mental effort throughout the task. Physiologically, this pattern suggests successive adjustments of attentional-executive resources during test execution. The FT protocol imposed motor control, strength, coordination, and postural stability, but did not incorporate concurrent cognitive tasks as a central component of the session. Thus, when faced with a predominantly inhibitory task such as the SCWT, the pupillary response after FT seems to have reflected greater variation in resource allocation over time.

This result is consistent with reviews on acute exercise, which show executive responses dependent on modality, intensity, and the cognitive domain assessed [46, 47]. It also aligns with the literature on cognitively engaging exercises [50]. Gu et al. (2019) [50], in a systematic review, observed that open-skill exercises tend to favor some components of cognition compared with closed-skill exercises, although with heterogeneity across studies. More closely related to the present work, Takahashi and Grove (2023) [51] compared an acute session of badminton and running at similar intensities and observed improved inhibitory control on the SCWT after badminton, without a corresponding increase in prefrontal activation measured by fNIRS [51]. The authors interpreted this pattern as

possible greater neural efficiency after an activity with higher perceptual and decisional demand [51]. In the present study, the difference between FT and BFT suggests that modulation of the pupillary response depended less on the motor variety of the session and more on the presence of cognitive-motor demands incorporated into the exercise.

The difference between the SCWT and N-back task reinforces this interpretation. The low-curvature pattern associated with BFT was more pronounced in the SCWT, whereas in the N-back task curvature values after FT and BFT were closer to each other and lower than after AT. This distinction suggests that the acute effects of the modalities are not uniform across all executive functions. Miyake et al. (2000) [52] proposed that executive functions share common components but show relative independence among inhibition, updating, and shifting [52]. The SCWT strongly depends on inhibitory control and interference resolution; the N-back task requires continuous maintenance and updating of information. The greater sensitivity of the SCWT to BFT may therefore reflect greater correspondence between the cognitive-motor demands incorporated into the session and the executive domain assessed by the task.

In BCS, this finding has particular implications. Cancer-related cognitive complaints frequently involve difficulty concentrating, mental slowing, cognitive fatigue, and greater effort to perform daily activities that were previously automatic [1, 5, 20]. Myers et al. (2019) [20] showed that BCS may present performance similar to healthy individuals on neuropsychological tests, but with greater mental effort indexed by pupillary response [20]. The data from the present study agree with this interpretation and go further by showing that the temporal dynamics of the pupillary response associated with mental effort can be acutely modulated by the type of exercise performed before the task.

The contribution of this work is to demonstrate that the relationship between behavioral performance and mental effort is modifiable by the organization of the exercise session. To our knowledge, this study provides the first empirical evidence of BFT in BCS, showing that a session structured with cognitive-motor complexity as part of the training dose produces a low-curvature pupillary trajectory during inhibitory control, without impairing behavioral performance. For the scientific community, these results add an acute intervention to a phenomenon previously described by Myers et al. (2019) [20]; for clinical practice, they suggest that the mental effort required to sustain executive tasks may constitute a measurable physiological target for exercise prescription.

Limitations and Future Research

Some limitations should be considered when interpreting these findings. First, the sample size was small and included post-treatment BCS with preserved functional mobility and stable clinical status, which may limit generalizability to survivors with greater functional impairment, active disease, or more recent treatment completion. Second, because the study compared three active exercise conditions, without a non-exercise control condition, the findings indicate differences between exercise modalities but do not allow conclusions about whether each modality differs from rest or usual daily activity. Third, integrated curvature was used as a complementary metric to quantify the temporal shape of the pupillary trajectories. Although this approach is consistent with the aim of analyzing the dynamic behavior of TEPR, its use in exercise-related pupillometry studies in cancer survivors is still emerging and requires replication.

The next step is to investigate whether this acute modulation is maintained with systematic repetition of BFT and whether it is associated with perceived daily-life outcomes, such as cognitive fatigue and self-reported cognitive complaints. Future studies should also explore whether longer executive tasks reveal patterns of accumulation, saturation, or decline in the pupillary response compatible with the Yerkes and Dodson (1908) [53] and with the

adaptive gain theory of the locus coeruleus-norepinephrine system proposed by Aston-Jones and Cohen (2005) [44].

CONCLUSION

This study demonstrated that AT, FT, and BFT produced similar acute effects on behavioral performance in executive tasks among BCS. However, the modalities differed in pupillary dynamics, indicating that equivalent performance was sustained with distinct levels of mental effort. BFT produced a more stable, low-curvature pupillary trajectory during inhibitory control, suggesting lower physiological demand and greater temporal stability in maintaining executive performance. These findings support pupillometry as a sensitive measure of acute exercise responses on mental effort and, to our knowledge, provide the first empirical evidence that BFT, structured with cognitive-motor complexity as part of the training dose, can acutely modulate executive effort in BCS.

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Competing Interests:

The authors declare that they have no relevant financial or non-financial interests to disclose.

Ethics Approval:

This study was approved by the Research Ethics Committee of the Federal University of Sergipe (approval no. 8.350.704). All procedures were conducted in accordance with the Declaration of Helsinki and Resolution no. 466/2012 of the Brazilian National Health Council.

Consent to Participate:

All participants provided written informed consent before the start of the study procedures.

Consent to Publish:

Not applicable. This manuscript does not contain identifiable individual data, images, or personal information.

Data Availability

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

Disclosure Statement:

The authors declare no conflicts of interest.

Author Contribution

DCSRV contributed to study conception, study design, data collection, data organization, interpretation of results, and writing of the original manuscript draft. LDSV contributed to data analysis, statistical procedures, interpretation of quantitative results, and critical revision of the manuscript. LMSC contributed to study planning and development of the experimental procedures. MRPM contributed to study conception, study planning, and development of the experimental procedures. HJT contributed to methodological discussion, interpretation of results, and critical revision of the manuscript. MESG contributed to study conception, study design, supervision, interpretation of results, and critical revision of the manuscript. All authors read and approved the final manuscript.

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Data Availability

The datasets generated and analyzed during the current study are not publicly available due to ethical and privacy restrictions involving human participants, but are available from the corresponding author on reasonable request.

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Figures

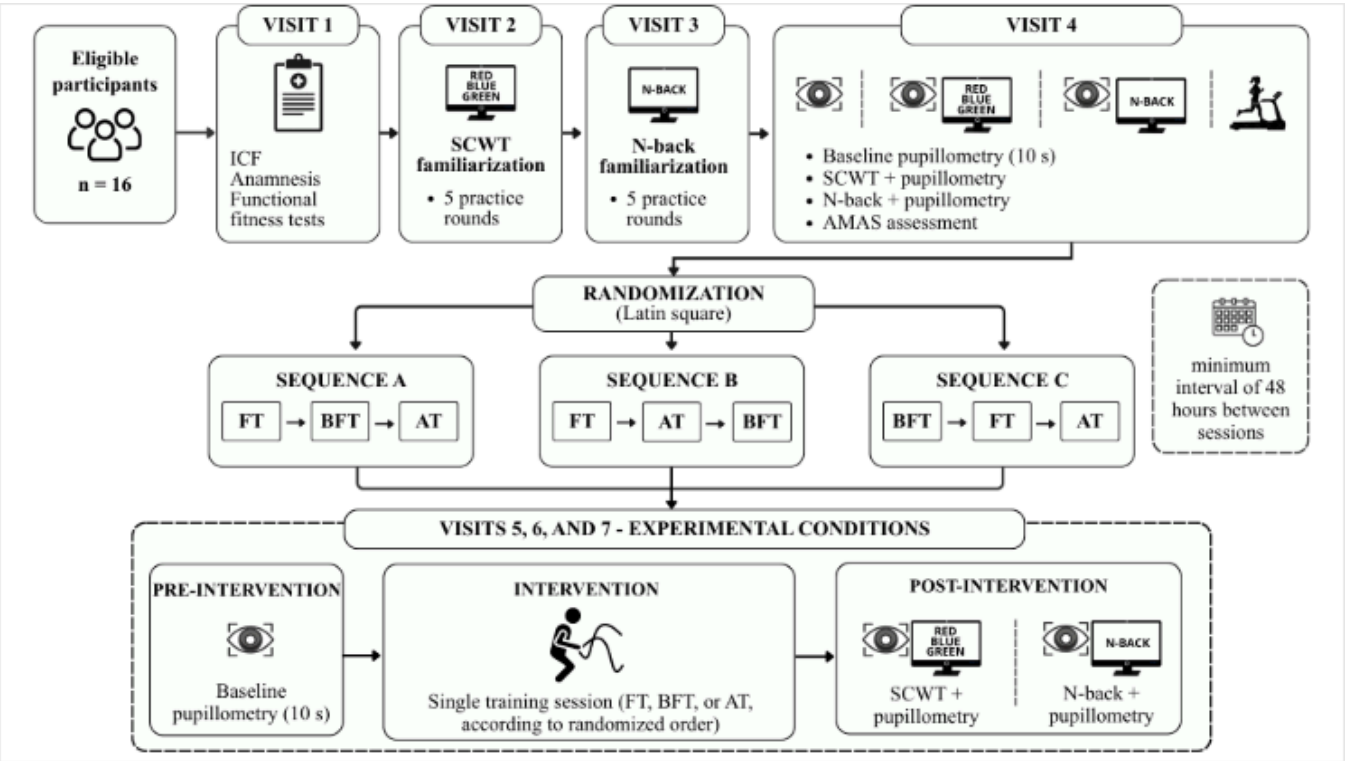


Figure 1

Experimental Design

Note: Flowchart of the experimental design. ICF: informed consent form; SCWT: Stroop Color and Word Test; N-back: working memory task; MAS: maximal aerobic speed; FT: functional training; BFT: Brain Functional Training; AT: aerobic training.

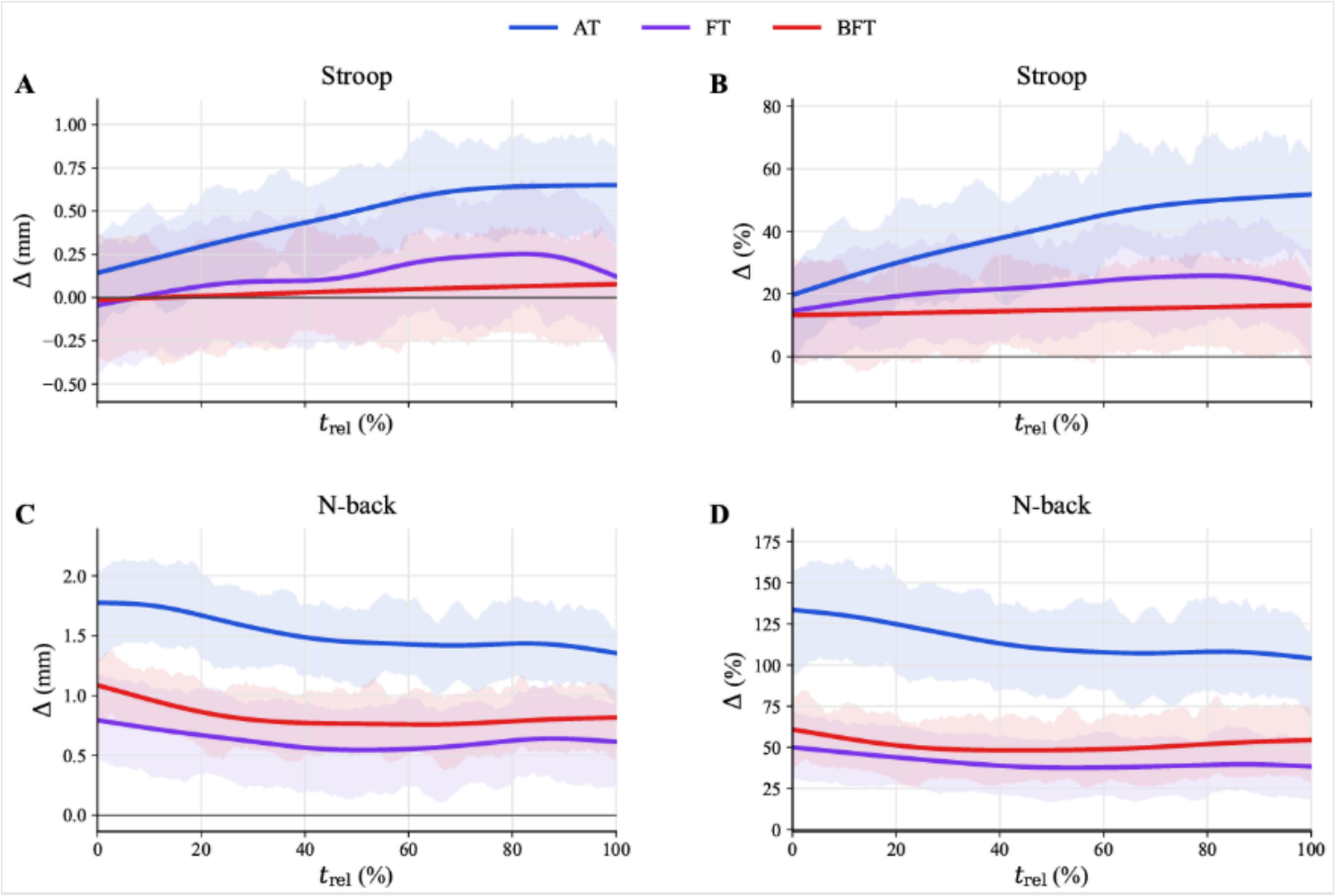


Figure 2

Temporal dynamics of the pupillary response during the SCWT and N-back task

Note: Estimated pupillary trajectories after the experimental conditions AT, FT, and BFT. Solid lines represent the mean temporal trajectories, and shaded areas represent the standard error of the mean. Panels A and C show the absolute change in pupil diameter relative to the baseline immediately preceding the cognitive test Δ (mm), whereas panels B and D show the corresponding percentage change Δ (%). The horizontal axis represents relative task time, normalized from 0 to 100%. SCWT: Stroop Color and Word Test; AT: aerobic training; FT: functional training; BFT: Brain Functional Training; SEM: standard error of the mean.

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- OnlineResource1.SupplementaryMaterialSUBMISSION.pdf