

# The magnitude of combined training-induced changes in executive functions is related to pre-training BDNF levels in middle-aged and older adults with Type 2 Diabetes Mellitus

João Gabriel da Silveira-Rodrigues (✉ [joaogabrielsrod@gmail.com](mailto:joaogabrielsrod@gmail.com))

UFMG <https://orcid.org/0000-0003-2646-5079>

Nathália Gardênia de Holanda Marinho Nogueira

UFMG <https://orcid.org/0000-0003-0286-7559>

Larissa Oliveira Faria

UFMG <https://orcid.org/0000-0002-4570-5368>

Daniele Sirineu Pereira

UFMG <https://orcid.org/0000-0002-4868-9244>

Danusa Dias Soares

UFMG <https://orcid.org/0000-0002-5705-8890>

---

## Research Article

**Keywords:** physical exercise, neurotrophins, inhibitory control, cognitive flexibility, cognition

**Posted Date:** April 26th, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-358254/v2>

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

[Read Full License](#)

---

**Version of Record:** A version of this preprint was published at Experimental and Clinical Endocrinology & Diabetes on June 14th, 2023. See the published version at <https://doi.org/10.1055/a-2069-4050>.

# Abstract

**Background:** Many cognitive functions are affected by Type 2 Diabetes Mellitus (T2DM). Aerobic plus resistance exercise training, known as combined training (CT), may mitigate or reverse the T2DM-related cognitive impairment by improving metabolic control. Brain-derived neurotrophic factor (BDNF) seems to modulate the cognitive functions of healthy and T2DM adults. However, the CT-effects on BDNF levels of T2DM subjects need to be better elucidated.

**Aim:** To analyze the effects of 8-week CT on circulating BDNF levels of T2DM subjects. Additionally, were investigated the relationship between BDNF levels and CT-induced changes in executive functions and long-term memory of T2DM subjects.

**Methods:** Thirty-five ( $63 \pm 8$  years old) T2DM subjects of both sexes were allocated to CT ( $n=17$ , thrice-weekly during 8 weeks) or control group (CONT,  $n=18$ ). Executive functions (evaluated through Trail making test, Stroop color task, and Digit Span), long-term memory (evaluated through the simplified version of Taylor Complex Figure Test), and plasma samples were analyzed pre- and post-intervention.

**Results:** CT induced higher improvements in executive functions composite z-score than CONT ( $d= 1.31$ ). BDNF levels were not statistically altered (pre-CT:  $179 \pm 88$  pg/ml; post-CT:  $148 \pm 108$  pg/ml; pre-CONT:  $163 \pm 71$  pg/ml; post-CONT:  $141 \pm 84$  pg/ml,  $p > 0.05$ ). However, pre-CT BDNF levels were positively related to CT-induced changes on executive functions composite z-score ( $r= 0.71$ ), inhibitory control ( $r= 0.58$ ) and cognitive flexibility ( $r= 0.56$ ).

**Conclusion:** CT improved executive functions and higher pre-training BDNF levels have been correlated to those CT-induced improvements on executive functions, independently of the training alterations in resting BDNF levels of T2DM subjects.

## Introduction

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder that impairs several metabolic pathways that participate in insulin signaling dysregulating glucose metabolism (DeFronzo et al. 2015). Impaired glucose metabolism affects several organic tissues, and the brain is one of them (Cherbuin and Walsh 2019). T2DM can accelerate the progressive changes in brain functioning and structure observed with the process of aging (Cherbuin and Walsh 2019). Epidemiological studies reported that T2DM increased the risk for mild cognitive impairment (MCI) and dementia at nearly 20% and 50%, respectively (Cheng et al. 2012). Furthermore, type 2 diabetic subjects with MCI are likely to develop dementia almost three years before those without MCI at the same age (Ma et al. 2014).

-  
Cognitive function refers to mental processes involved in acquiring knowledge, manipulating information, and reasoning. Cognitive functions include the domains of memory and learning, attention, processing

speed, language abilities, and executive functions (Palta et al. 2014). From a healthcare perspective, preserved cognitive functions are crucial to the T2DM treatment, including blood glucose monitoring, medication adherence, reducing stress, adopting healthy behaviors, caring for both skin and feet (Munshi 2017). Poor diabetes self-care management (*e.g.*, blood glucose monitoring and self-management of prescribed drug therapy), low diabetes knowledge, along higher help care needs are observed in those T2DM subjects with the lowest cognitive screening scores (Sinclair et al. 2000). Furthermore, older adults with T2DM and MCI are less likely to adhere to exercise and diet compared to their cognitively preserved peers (Feil et al. 2012). Impaired performance in some neurocognitive domains, such as executive functions and long-term memory, has been extensively observed in T2DM subjects (Palta et al. 2014; Sadanand et al. 2016). While low levels of executive function somehow increase the risk of older adults developing frailty and disability (Johnson et al. 2007), higher executive function scores may preserve functionality otherwise. T2DM subjects with the highest memory scores are more likely to adhere to prescribed drug therapy (Vedhara et al. 2004), improving their metabolic control and preventing T2DM-related negative outcomes. Thus, therapeutic strategies focused on improving cognitive functions may modify the course of T2DM by preventing or mitigating the progression of cognitive damages (Sharma et al. 2020).

Exercise training is a promising and low-cost non-pharmacological therapy in preventing and treating many diseases, including cardiovascular diseases, certain types of cancer, and T2DM (Booth et al. 2012). Regarding cognitive effects, exercise training improves the long-term memory of cognitively normal older adults and executive functions of healthy and older adults with MCI (Sanders et al. 2019). We have recently shown that combined exercise training also enhances some cognitive functions of middle-aged and older adults with T2DM (Silveira-Rodrigues et al. 2021), highlighting memory and executive functions (Cooke et al. 2020). However, a recent Consensus Statement from the American College of Sports Medicine pointed out a paucity of data on the underpinning mechanisms involved in exercise training-induced cognitive improvement in T2DM subjects (Kanaley et al. 2022).

Brain-derived Neurotrophic Factor (BDNF) is a protein member of the neurotrophins family involved in several brain physiological processes. When binds to tropomyosin receptor kinase B (TrkB), BDNF exerts its central function by triggering neurons growth and survival and improving their resistance to damage (Rozanska et al. 2020). Due to its actions in modulating synaptic transmission, synaptic plasticity, neurogenesis, learning, and memory processes, BDNF is assumed as a biomarker that reflects mnemonic symptoms in various pathologic conditions (Miranda et al. 2019). Several cross-sectional studies reported lower circulating BDNF levels in T2DM subjects compared to non-T2DM controls (Geroldi et al. 2006; Krabbe et al. 2007; Fujinami et al. 2008; Zhen et al. 2013; Sun et al. 2018). Indeed, reduced serum BDNF levels in middle-aged and older adults with T2DM were not only accompanied by poor attentional and long-term memory performance (Zhen et al. 2013) but also increased by at least 50% the

risk for developing MCI (Sun et al. 2018). Thus, BDNF appears to play a substantial role in T2DM-related cognitive dysfunctions.

BDNF participates in the muscle-brain crosstalk since skeletal muscle and other tissue release BDNF after an exercise bout increasing their circulating and central levels (Walsh and Tschakovsky 2018). As it crosses the blood-brain barrier through a rapid saturable transporter system, peripheral synthesized BDNF could enter the central nervous systems (Pan et al. 1998) elevating the BDNF levels in the brain (Walsh and Tschakovsky 2018). Circulating BDNF levels increase after a single exercise bout in T2DM subjects (Brinkmann et al. 2017) and other populations (Szuhany et al. 2015). However, the effects of exercise training (long-term repeated exercise bouts) on circulating BDNF of T2DM subjects need to be further investigated. A long-term exercise training program failed to demonstrate significant changes in serum BDNF of adults and older with T2DM (Swift et al. 2012). Moreover, to the best of our knowledge, the relationship between BDNF levels and training-induced cognitive improvements in T2DM remains poor elucidated. Assuming that BDNF and its receptors TrkB are expressed in the prefrontal cortex and hippocampus (Neeper et al. 1996; Rasmussen et al. 2009), brain areas that encompass the executive functions and long-term memory, it is tempting to suggest that BDNF levels can mediate the training-induced improvements in these cognitive functions.

Therefore, this study aimed to analyze the effects of 8 weeks of combined (aerobic and resistance) training on circulating BDNF levels of T2DM subjects. Additionally, it was investigated whether both pre-training and training-induced changes in BDNF levels were related to training-induced changes on executive functions and long-term memory. It was hypothesized that BDNF levels would be related to training-induced changes in cognitive functions of T2DM subjects.

## **Material & Methods**

### *Ethical care*

The study protocol followed Helsinki's Declaration and was approved by the Research ethics committee of Universidade Federal de Minas Gerais/Brazil (no. 2.067.044/66804817.8.0000.5149). This study was prospectively registered on October 23, 2017, in the Brazilian Registry of Clinical Trial (register no. RBR86hfz5, WHO international clinical trials registry platform no. U1111-1202-6942). Following an explanation of the experimental procedures, participants signed a consent form to be included in this study. Recruitment was performed by phone contact between February and May/17.

### *Participants and sample size determination*

Sample size were determined based on the changes induced by combined training on executive function parameters (Liu-Ambrose et al. 2010). The following parameters were inputted in G\*Power v3.0.10 (Universität Kiel, KI, GER) to determine sample size: (1)  $\alpha=5\%$ ; (2) power  $(1-\beta) = 0.7$ ; (3) allocation rate of 1:1 and (4) aimed *Cohen's d*= 0.8 (large effect size) in a one-tailed test (considering that CT improves executive functions). Thereby, a minimum of 16 subjects in each experimental group was obtained.

Middle-aged and older adults (aged between 50-79 years) of both sexes and up to 2 years of T2DM diagnosis (defined by the American Diabetes Association criteria). Additional requirements were: being literate; had normal or corrected visual and auditory functions; being physically inactive during the last three months; and were absent of musculoskeletal conditions (See sample characteristics in Table 1). Exclusion criteria were: severe autonomic or peripheral neuropathy; severe diabetic retinopathy; decompensated heart failure; an attendance rate of less than 60% of the total of 24 CT training sessions. Seventeen subjects entered combined training (CT) and eighteen in control (CONT) group. Four subjects left the study (one in CT for personal reasons; and three in CONT, one for lower limb fracture in daily living activity, another two for the impossibility to be contacted by phone number). In two participants of CONT, although cognitive tests were performed, it was not possible to assess BDNF levels. Therefore, 31 participants were included in the cognitive analysis, and 29 in BDNF levels analysis (Figure 1).

(FIGURE 1 HERE)

### *Experimental design*

The present clinical trial was composed by two parallel groups, allocated at 1:1. Pre-training data were assessed in three moments, interspaced by at least 48h. On day one, the volunteers were cognitively screened and answered a questionnaire about health status and sociodemographic information. At the second occasion, blood samples and blood pressure were assessed. On day three, cognitive tasks and other baseline parameters were performed. After these procedures, CT-group performed 8 weeks of combined training and CONT-group was guided to maintain their life routine. At least 72 hours after the last training session, post-training blood samples and cognitive tasks were assessed. All the volunteers should avoid intense physical activity, caffeinated or alcoholic beverages, and to maintain their habitual food and water ingestion in the 24 hours before the experimental procedures.

### *Baseline parameters*

Blood pressure was assessed by a digital calibrated device (OMRON HEM-7113©, KY, JAPAN). Waist circumference was measured in duplicate at the narrowest point between the rib cage and hips, considering the mean value for analysis. A Six-minutes walk test was used to evaluate the functional capacity. The participants should walk in a 30-m corridor for six minutes at a maximal speed as they could. The Montreal Cognitive Assessment (MoCA), a cognitive screening instrument that assesses numerous cognitive functions, allowing the identification of mild cognitive impairment and dementia in older adults, was used. MoCA is sensitive for screening cognitive impairments, validated, and translated for the Brazilian subjects (Memória et al. 2013). Participants were classified according to compatible score for mild cognitive impairment or dementia, using adjusted cut-offs for age and years of education (Memória et al. 2013). The assumed cut-off values were -1.0 and -2.0 z-score for the compatible score to mild cognitive impairment and dementia, respectively (Memória et al. 2013).

### *Combined training program (CT)*

The CT-protocol followed the recommendations of the American Diabetes Association for aerobic and resistance exercise in subjects with T2DM (Kanaley et al. 2022). During 8 weeks, subjects performed thrice-weekly non-consecutive sessions. The exercise protocol is detailed in a previous study from our group (Silveira-Rodrigues et al. 2021).

### *Executive functions and data transformation of cognitive task performance*

Executive functions are the suite of processes that underlie goal-directed self-regulatory behaviors (Diamond 2013). The three components of the executive functions' core are described below. Cognitive flexibility refers to the creative process and comprises the ability to alternate the perspective of analysis of a task or situation. Inhibitory control encompasses the ability of attention, behavior, and emotion control to mitigate the intervention of distractors. Working memory refers to the ability to hold information in mind and work mentally as math reasonings or reorder a task list, as an example (Diamond 2013).

Cognitive flexibility was assessed through the Trail making test (TMT), inhibitory control by the Stroop color task (SCT) and working memory by Digit Span (DS). The interference score (Nagamatsu et al. 2012) ] assessed the specific-domain executive function performance by subtracting the values of the incongruent trial from the neutral trial.. The cognitive flexibility score was assessed by TMT-A minus TMT-B. Inhibitory control score through composite z-score of SCT-congruent and SCT-incongruent (total time + (2 \* mean time per word \* error number). Working memory through DS-reverse minus DS-direct. Executive function composite z-score represents the mean of cognitive flexibility, inhibitory control, and working

memory z-scores. If the volunteer lost or was unable to perform any task, the arithmetic means of the other task parameters were determined as the individual composite z-score.

The cognitive task parameters were z-score transformed as adopted previously (Espeland et al. 2017)

through the equation:  $Z = \frac{x-X}{\sigma}$ , where x: individual value, X: sample mean and  $\sigma$ : group standard deviation. Considering that in TMT and SCT the lower time for answering these tasks represents better performance, then, the interference z-scores were multiplied by -1 (Nagamatsu et al. 2012).

### *Long-term memory*

Memory refers to the capacity of retaining and manipulating acquired previous information through neural plasticity (Squire 2004). The Taylor Complex Figure Test in a simplified version (Paula et al. 2016), a task involving visuospatial abilities and episodic memory recall, was employed to assess long-term memory. Individuals' scores were obtained through the difference between the immediate copy score and the delayed 30min-copy score. In this case, lower values represented better performance.

### *Blood Samples and biochemical analysis*

Samples were collected 72h after the last familiarisation session (pre-training) and after the last CT-session (post-training). After 12h of fasting and in the morning, blood samples were collected in heparinized tubes and stored in styrofoam until centrifugation (10 min, 3500rpm, and 4°C) for plasma separation. After that samples were stored at -80°C in aliquots of 100  $\mu$ l until analysis. Plasma BDNF levels were quantified by sandwich ELISA specific kit (DY248 DuoSet, R&D Systems™, MN, USA) according to the manufacturer's instructions. A single plate was blocked for 3 h in reagent diluent (1% bovine serum albumin (BSA)/ phosphate-buffered saline (PBS)) and incubated for nearly 12 h with 100  $\mu$ l of samples at 4° C. Samples were diluted 1:64 to the standard curve fit (detection range: 23-1500 pg/ml). The baseline blood glucose, lipids, and fructosamine were quantified by the enzymatic colorimetric technique using specific kits (Gold Analisa™, MG, BR). Plasma insulin was quantified by chemiluminescence (Siemens Centaur™, NY, USA). Metabolic syndrome was assumed considering a previously reported NCEP-ATP III criteria (Expert Panel on Detection, Evaluation, 2001).

### *Statistical analysis*

Normality and homoscedasticity were tested with Shapiro-Wilk's and Levene's tests, respectively. Chi-square tests were conducted for ordinal and nominal variables (sample characteristics). For normally

distributed variables, it was conducted parametric analyses. Sample characteristics and plasmatic BDNF levels were presented in mean  $\pm$  standard deviation (SD). Student's t-test for independent samples (two-tailed) compared the changes in executive function composite z-score and interference scores in both groups after 8-weeks. Two-way ANOVA with repeated measures was used to compare the BDNF levels between time and group. Three-way ANOVA was performed to compare the BDNF between time, group, and age. Simple linear regression analyses were used to determine the relationship between plasmatic BDNF levels with CT-induced changes in executive functions and long-term memory. Additionally, Cohen's d was calculated:  $(x^1 - x^2) / (\sigma \text{ pooled})$ , where  $x^1$  was the pre-training mean,  $x^2$  the post-training mean value, and  $\sigma$  the pooled standard deviation of these groups. To observe the clinical relevance of the treatment on the studied parameters was classified according to the effect size (Cohen's d) as trivial if  $d < .2$ , small:  $d = .2$  to  $.5$ ), medium  $d = .5$  to  $.8$ , and large  $d > .8$ . A posteriori power was calculated for BDNF levels using G\*Power v3.0.10 (Universität Kiel, KI, GER). Data were analyzed in GraphPad Prism v5.0 (GraphPad Software Inc., CA, USA). The significance level was 5%.

## Results

The groups were similar regarding sociodemographic, functional, cognitive screening, clinical, and biochemical parameters ( $p > 0.05$  for all). According to criteria for Brazilians (Apolinario et al. 2018), nearly three-quarters of the sample were cognitively normal, 23% had a compatible score to MCI, and merely 3% had dementia. It was detected that 75% of the CT and 93% of CONT subjects had metabolic syndrome by attaining three or more risk determinants for metabolic syndrome presence according to NCEP-ATP III criteria (Expert Panel on Detection, Evaluation 2001).

Table 1: Pre-training sample characteristics (Mean  $\pm$  SD or absolute and relative value)

Parameter	CT (n= 16)	CONT (n= 15)	p value
Age (years)	63.9 ± 7.7	63.3 ± 7.8	0.98&
Time of T2DM diagnosis (years)	11.3 ± 7.7	14 ± 10.1	0.50&
HOMA-IR	3.8 ± 2.8	4.3 ± 2.7	0.34&
Fructosamine (mmol/ml)	249 ± 61	259 ± 54	0.65&
Six-minutes walk test (m)	527 ± 88	516 ± 80	0.72&
Education time (years)	9.4 ± 4.7	8.9 ± 5.1	0.53&
MoCA score	20.3 ± 5.4	21.8 ± 3.9	0.70&
Cognitively normal	10 (63%)	13 (80%)	0.95#
Mild cognitive impairment	5 (31%)	2 (20%)	
Dementia	1 (6%)	0 (0%)	
Sex (females)	10 (63%)	14 (93%)	0.08#
<i>MetS NCEP-ATP III criteria</i>			
HHD (SAP: <135, DAP: <85mmHg)	8 (50%)	10 (67%)	0.57#
WC (W: >88, M: >102cm)	11 (69%)	13 (87%)	0.39#
TG (>150 mg/dl)	15 (94%)	13 (87%)	0.60#
HDL-c (W: >50, M: >40 mg/dl)	5 (31%)	4 (27%)	0.99#
FG (>110 mg/dl)	15 (94%)	14 (93%)	0.99#
Above than 3 factors	12 (75%)	14 (93%)	0.33#

Note: CONT: control group, CT: Combined training group, DAP: Diastolic arterial pressure, FG: Fasting glucose, HDL-c: High-density lipoprotein cholesterol, HHD: Hypertensive heart disease, HOMA-IR: Homeostatic model assessment, MetS: Metabolic syndrome, MoCA: Montreal Cognitive Assessment, SAP: Systolic arterial pressure, TG: Triglycerides, WC: Waist circumference, *NCEP-ATP III criteria*: National cholesterol education program adult treatment panel III. & *Student's* paired T-test, # *Chi-square* test.

Plasmatic BDNF levels (pre-CT: 179 ± 88 pg/ml; post-CT: 148 ± 108 pg/ml; pre-CONT: 163 ± 71 pg/ml; post-CONT: 141 ± 84 pg/ml) didn't show main effects for time ( $F_{(1,53)} = 2.64$ ;  $p = 0.12$ ), group ( $F_{(1,53)} = 0.08$ ;  $p = 0.78$ ) or interaction ( $F_{(1,53)} = 0.32$ ;  $p = 0.58$ ) (Figure 2). A posteriori power ( $1-\beta$ ) of BDNF analysis was 0.23. Considering that training-effect on BDNF levels may be modulate by age (Leckie et al. 2014), we decided to analyze subjects above ( $n = 8$  in both groups) and below 65 years old ( $n = 8$  and 5, in CT and CONT, respectively). No main effects or interaction ( $F > 1.16$ ,  $p > 0.29$  for all) were observed in plasmatic BDNF levels neither in older adults (pre-CT: 180 ± 106 pg/ml; post-CT: 155 ± 113 pg/ml; pre-CONT: 187 ± 110 pg/ml; post-CONT: 145 ± 69 pg/ml) nor in middle-aged adults (pre-CT: 177 ± 74 pg/ml; post-CT: 141 ± 109 pg/ml; pre-CONT: 148 ± 31 pg/ml; post-CONT: 150 ± 59 pg/ml).

(FIGURE 2 HERE)

The CT improved executive functions, as demonstrated by the higher reductions in composite executive function z-score (CT:  $0.38 \pm 0.58$  z, CONT:  $-0.46 \pm 0.70$  z,  $d= 1.31$ ,  $t= 3.59$ ,  $df= 28$ ,  $p= 0.001$ ) (Figure 3). Also, CT showed higher changes when compared with the control group in interference scores of inhibitory control (CT:  $-0.10 \pm 0.20$  s, CONT:  $0.12 \pm 0.31$  s,  $d= 0.87$ ,  $p= 0.03$ ) and working memory interference scores (CT:  $-0.33 \pm 0.98$  s, CONT:  $0.05 \pm 0.91$  s,  $d= 0.40$ ,  $p= 0.03$ ), but not for cognitive flexibility interference scores although a higher effect size there was obtained (CT:  $-0.45 \pm 0.76$  s, CONT:  $0.19 \pm 0.48$  s,  $d= 0.96$ ,  $p= 0.15$ ). On the other hand, the changes on long-term memory z-score were not different between groups ( $d= 0.22$ ,  $t= 0.56$ ,  $df= 25$ ,  $p= 0.56$ ) as we previously described (Silveira-Rodrigues et al. 2021).

(FIGURE 3 HERE)

Interestingly, pre-training BDNF levels were correlated ( $r= 0.71$ ,  $r^2= 50.4\%$ ;  $p< 0.01$ ; 95% CI: 0.33-0.89;  $d= 0.62$ ; a *posteriori* power: 0.71) to CT-induced changes on composite executive function z-score (Figure 4). Additional analysis was performed considering the three core executive functions separately. Pre-training BDNF levels were significantly related to inhibitory control ( $r= 0.58$ ,  $r^2= 33.6\%$ ;  $p= 0.02$ ) and cognitive flexibility ( $r= 0.56$ ,  $r^2= 31.4\%$ ;  $p= 0.04$ ), but not with working memory ( $p= 0.31$ ) and long-term memory ( $p= 0.55$ ).

Additionally, there was tested whether the CT-induced change on BDNF levels (post minus pre-CT) are correlated to composite z-score of executive function ( $p= 0.20$ ), inhibitory control ( $p= 0.30$ ), cognitive flexibility ( $p= 0.33$ ), working memory ( $p= 0.51$ ), or long-term memory ( $p= 0.77$ ), but no significant correlations were found for all.

(FIGURE 4 HERE)

## Discussion

The main finding of our study was that CT-induced ameliorations on the components of executive function of T2DM subjects as observed by the changes in executive functions composite scores, and those alterations correlated positively with pre-training plasma BDNF levels. Conversely, long-term memory appears not to be related to pre-training plasmatic BDNF levels.

Despite recent progress in the T2DM diagnosis and treatment, little attention is given to the chronic complications which may impair the quality of life and self-management of T2DM. Growing and novel evidence focuses on the development of course-modifying therapies to counteract T2DM-related cognitive dysfunction (Biessels and Despa 2018). A recent meta-analysis highlights the trifling amount of published studies regarding the exercise training effects on cognitive outcomes of T2DM subjects (Cooke et al. 2020). Our results show that CT induced positive effects on executive functions of T2DM adults and older. The executive functions have been related to general health (see Diamond, 2013) (Diamond 2013), and in T2DM subjects it has not been different (Sadanand et al. 2016). The self-management of T2DM, lower hospitalization number (Sinclair et al. 2000), adherence to diet and exercise (Feil et al. 2012), depends on cognitive health preservation. Furthermore, executive functions were a better predictor of functional decline and mortality of older women than global cognition (Johnson et al. 2007). The executive functions enhancement by exercise training can induce other health benefits. For example, a one-year resistance training-induced improvements in executive function contributed to the maintenance of physical activity over the following year (Best et al. 2014). However, studies that concomitantly explore the mechanisms underlying the training-induced cognitive benefits in T2DM subjects are scarce.

The present study failed to demonstrate significant changes in BDNF levels between T2DM subjects in the trained and control group. Only single (Rasmussen et al. 2009) or twice aerobic exercise bouts (Neeper et al. 1996) raise the mRNA BDNF expression in the prefrontal cortex and hippocampus. An accumulating body of evidence suggests that BDNF modulates some exercise effects on cognition (Intlekofer et al. 2013; Tang et al. 2017). In humans, due to the inability to assess brain BDNF mRNA expression, current studies often measured the serum or plasma circulating BDNF levels which are strongly correlated to brain BDNF levels (Sartorius et al. 2009). Tang *et al.* (2017) investigated the effects of exercise training on the memory of diabetic rats, revealing that resistance training improves not only the learning performance of rats but also upregulates the expression of BDNF mRNA and its receptor TrkB in the hippocampus. They suggested that BDNF may also be involved in training-induced cognitive benefits in the face of metabolic alterations present in diabetes. However, according to a recent meta-analysis (Jamali et al. 2020), the effects of exercise training in BDNF levels of adults and older with T2DM are still scarce and inconclusive. A meta-analysis

revealed that an exercise training program (lasting from a week to months) has a lower capability to increase the circulating BDNF levels compared to a single bout of exercise (Szuhany et al. 2015). In T2DM subjects, similar results have been reported, as when a single bout of aerobic exercise increased circulating BDNF levels (Brinkmann et al. 2017), nine months of aerobic, resistance, or combined training didn't increase serum BDNF in 30-75 years old T2DM subjects (Swift et al. 2012). Furthermore, six months of aerobic training also didn't change plasma BDNF levels of older adults with glucose intolerance (Baker et al. 2010). Thus, corroborating with previous findings, our results showed that a

shorter training period (8-week of CT) also does not significantly change resting plasmatic BDNF levels in middle-aged and older T2DM subjects.

In an unprecedented way, this study showed that pre-training plasmatic BDNF levels were not only positively correlated with CT-induced changes on executive function (composite z-score) but were also able to explain one-half of the variance in CT-induced changes on the executive functions.

SA single bout of prolonged aerobic exercise at low to moderate intensity briefly raised the plasmatic BDNF levels in humans, but one hour after exercise these levels returned to baseline (Rasmussen et al. 2009). However, an evident increase in the expression of BDNF mRNA in the prefrontal cortex and hippocampus occurred in mice immediately after prolonged aerobic exercise (Rasmussen et al. 2009). Nonetheless, the peak of BDNF mRNA expression in both brain regions occurred around two hours after exercise cessation and remained upregulated for the following 24h (Rasmussen et al. 2009). In another study, after three weeks of voluntary exercise, brain BDNF mRNA expression increased in mice, which was paralleled to memory improvements (Intlekofer et al. 2013). However, when the BDNF synthesis was blocked, the exercise-induced improvements in mice's memory didn't occur, suggesting that the cognitive amelioration was BDNF-dependent (Intlekofer et al. 2013). Likewise, higher serum BDNF levels were accompanied by higher increases in functional connectivity in the parahippocampus and middle temporal gyrus of middle-aged and older adults that performed 12 months of a training program focusing on flexibility, toning, and balance (Voss et al. 2013). Taken together, all these results endorse that the repeated transitory elevation of circulating BDNF levels after a single bout of physical exercise is a substantial contributor to the exercise-induced cognitive benefits, even without changing the circulating BDNF levels at rest. Therefore, it is possible that the higher plasmatic BDNF basal levels may potentially favored the CT-induced cognitive improvements observed in the T2DM subjects.

It is tempting to speculate that regarding basal BDNF levels there may potentially exist an "optimal window" of opportunity that can boost up exercise-induced improvements in executive functions in T2DM subjects. As it is known, T2DM subjects show lower basal BDNF levels than non-diabetic controls (Geroldi et al. 2006; Krabbe et al. 2007; Fujinami et al. 2008; Zhen et al. 2013; Sun et al. 2018), and this neurotrophic profile (*i.e.* inferred by BDNF levels) seems to be related to the metabolic disruption observed in these diabetic subjects (Geroldi et al. 2006; Levinger et al. 2008; Hristova 2013). For example, those with higher risk factors for metabolic syndrome showed higher basal plasmatic BDNF levels than those with the lowest risk factors (Levinger et al. 2008). Also, higher BDNF levels are reported in the early stages, whereas lower BDNF levels are reported in the late stage of T2DM (Geroldi et al. 2006; Hristova 2013). A study with animals showed that cerebral BDNF modulates glucose metabolism. The exogenous intracerebroventricular administration of BDNF inhibited hepatic gluconeogenesis, hence, relieving

hyperglycemia in the T2DM murine model, even without explaining the exact neuronal mechanisms involved (Meek et al. 2013). Akin, in our investigation, 75% of the sample studied attained multiple criteria for metabolic syndrome (Expert Panel on Detection, Evaluation 2001). *The Neurotrophic Theory* proposed by Hristova (2013) postulated that the early raises in BDNF levels observed in subjects with a higher risk factor for metabolic syndrome consist of an organic attempt to counteract the initial T2DM pathophysiology impairments comprising altered glucose metabolism and insulin signaling. Thence, we might suggest that the higher pre-training circulating BDNF levels may have provided an advantage for the T2DM subjects to obtain the exercise-induced improvements on executive functions when compared to the non-exercised ones.

Noteworthy, the subcomponents of executive functions were differently related to pre-training plasma BDNF levels. Higher inhibitory control and cognitive flexibility were positively correlated to higher pre-training BDNF levels.

However, the exercise-induced improvements in working memory and episodic long-term memory were unrelated to pre-training BDNF levels. It has already been shown that BDNF was crucial to memory development in a rodent model (Intlekofer et al. 2013). A previous study reported that serum BDNF levels correlated to episodic and semantic memory of T2DM subjects (Zhen et al. 2013), contrasting our findings. Indeed, memory is a complex system with some subdivisions, encompassing ultrarapid, short-term, and long-term memories. Long-term memory consists of storing information for late use and are separated into declarative and non-declarative memories. Declarative memory, in turn, is divided into semantics, which comprises ideas and concepts not drawn from personal experience, and episodic memory that is dependent on a specific event (Squire 2004). Working memory is one of the three core executive functions, composed of verbal and visuospatial working memory (Diamond 2013). The main difference between working and short-term memory is their component of manipulating information in the mind (Diamond 2013). In our study, both visuospatial episodic and verbal working memories were not significantly related to circulating pre-training BDNF levels. However, two main aspects should be considered. Firstly, animal studies measure the expression of the brain BDNF mRNA, which is impossible in human in-vivo studies. This might be relevant since, in response to an acute exercise session, the time to increase brain BDNF levels is longer than that observed for serum or plasma levels (Rasmussen et al. 2009). Secondly, our study assessed long-term memory by the adapted Taylor Complex Figure test, which only assesses episodic visuospatial abilities. Also, the working memory test used only recognizes the verbal component of working memory. Thus, the assessment of other memory components such as semantic and visuospatial memories should be included in future investigations. It would better explain the relationship between circulating baseline BDNF levels and putative exercise-induced improvements in memory.

This study has some limitations. Although sample size determination had been based on executive function variables, a *posteriori* power of longitudinal changes in plasmatic BDNF levels was 23%, suggesting a considerable likelihood of type II error occurrence. It can be due to the age and cognitive performance heterogeneity of our sample. Also, this study used a commercial enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems™) that does not recognize proBDNF, a molecule that antagonizes mature BDNF in their actions in the central nervous system. Further, most study participants underwent medication therapy, which might modulate plasmatic BDNF levels. Future studies including larger sample size can clarify the exercise training effects under distinct baseline BDNF levels.

## Conclusions

The magnitude of combined-training induced changes in executive functions was directly related to the pre-training BDNF levels, without altering the resting plasma levels of this neurotrophin in T2DM subjects.

## References

- Apolinario D, dos Santos MF, Sasaki E, et al (2018) Normative data for the Montreal Cognitive Assessment (MoCA) and the Memory Index Score (MoCA-MIS) in Brazil: Adjusting the nonlinear effects of education with fractional polynomials. *Int J Geriatr Psychiatry* 33:893–899. <https://doi.org/10.1002/gps.4866>
- Baker LD, Frank LL, Foster-Schubert K, et al (2010) Aerobic Exercise Improves Cognition for Older Adults with Glucose Intolerance, A Risk Factor for Alzheimer's Disease. *J Alzheimer's Dis* 22:569–579. <https://doi.org/10.3233/JAD-2010-100768>
- Best JR, Nagamatsu LS, Liu-Ambrose T (2014) Improvements to executive function during exercise training predict maintenance of physical activity over the following year. *Front Hum Neurosci* 8:1–9. <https://doi.org/10.3389/fnhum.2014.00353>
- Biessels GJ, Despa F (2018) Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev Endocrinol* 14:591–604. <https://doi.org/10.1038/s41574-018-0048-7>
- Booth FW, Roberts CK, Laye MJ (2012) Lack of Exercise Is a Major Cause of Chronic Diseases. In: *Comprehensive Physiology*. John Wiley & Sons, Inc., Hoboken, NJ, USA, pp 1143–1211
- Brinkmann C, Schäfer L, Masoud M, et al (2017) Effects of Cycling and Exergaming on Neurotrophic Factors in Elderly Type 2 Diabetic Men – A Preliminary Investigation. *Exp Clin Endocrinol Diabetes* 125:436–440. <https://doi.org/10.1055/s-0043-103967>
- Cheng G, Huang C, Deng H, Wang H (2012) Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern Med J* 42:484–491. <https://doi.org/10.1111/j.1445-5994.2012.02758.x>

- Cherbuin N, Walsh EI (2019) Sugar in mind: Untangling a sweet and sour relationship beyond type 2 diabetes. *Front Neuroendocrinol* 54:100769. <https://doi.org/10.1016/j.yfrne.2019.100769>
- Cooke S, Pennington K, Jones A, et al (2020) Effects of exercise, cognitive, and dual-task interventions on cognition in type 2 diabetes mellitus: A systematic review and meta-analysis. *PLoS One* 15:1–18. <https://doi.org/10.1371/journal.pone.0232958>
- DeFronzo RA, Ferrannini E, Groop L, et al (2015) Type 2 diabetes mellitus. *Nat Rev Dis Prim* 1:15019. <https://doi.org/10.1038/nrdp.2015.19>
- Diamond A (2013) Executive Functions. *Annu Rev Psychol* 64:135–168. <https://doi.org/10.1146/annurev-psych-113011-143750>
- Espeland MA, Lipska K, Miller ME, et al (2017) Effects of Physical Activity Intervention on Physical and Cognitive Function in Sedentary Adults With and Without Diabetes. *J Gerontol A Biol Sci Med Sci* 72:861–866. <https://doi.org/10.1093/gerona/glw179>
- Expert Panel on Detection, Evaluation and T of HBC in A (2001) Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA J Am Med Assoc* 285:2486–2497. <https://doi.org/10.1001/jama.285.19.2486>
- Feil DG, Zhu CW, Sultzer DL (2012) The relationship between cognitive impairment and diabetes self-management in a population-based community sample of older adults with Type 2 diabetes. *J Behav Med* 35:190–199. <https://doi.org/10.1007/s10865-011-9344-6>
- Fujinami A, Ohta K, Obayashi H, et al (2008) Serum brain-derived neurotrophic factor in patients with type 2 diabetes mellitus: Relationship to glucose metabolism and biomarkers of insulin resistance. *Clin Biochem* 41:812–817. <https://doi.org/10.1016/j.clinbiochem.2008.03.003>
- Geroldi D, Minoretti P, Emanuele E (2006) Brain-derived neurotrophic factor and the metabolic syndrome: More than just a hypothesis. *Med Hypotheses* 67:195–196. <https://doi.org/10.1016/j.mehy.2006.02.001>
- Hristova MG (2013) Metabolic syndrome - from the neurotrophic hypothesis to a theory. *Med Hypotheses* 81:627–634. <https://doi.org/10.1016/j.mehy.2013.07.018>
- Intlekofer KA, Berchtold NC, Malvaez M, et al (2013) Exercise and sodium butyrate transform a subthreshold learning event into long-term memory via a brain-derived neurotrophic factor-dependent mechanism. *Neuropsychopharmacology* 38:2027–2034. <https://doi.org/10.1038/npp.2013.104>
- Jamali A, Shahrbanian S, Morteza Tayebi S (2020) The Effects of Exercise Training on the Brain-Derived Neurotrophic Factor (BDNF) in the Patients with Type 2 Diabetes: A Systematic Review of the Randomized Controlled Trials. *J Diabetes Metab Disord* 19:633–643. <https://doi.org/10.1007/s40200-020-00529-w>

- Johnson JK, Lui L-Y, Yaffe K (2007) Executive Function, More Than Global Cognition, Predicts Functional Decline and Mortality in Elderly Women. *Journals Gerontol Ser A Biol Sci Med Sci* 62:1134–1141. <https://doi.org/10.1093/gerona/62.10.1134>
- Kanaley JA, Colberg SR, Corcoran MH, et al (2022) Exercise/Physical Activity in Individuals with Type 2 Diabetes: A Consensus Statement from the American College of Sports Medicine. *Med Sci Sport Exerc* 54:353–368. <https://doi.org/10.1249/MSS.0000000000002800>
- Krabbe KS, Nielsen AR, Krogh-Madsen R, et al (2007) Brain-derived neurotrophic factor (BDNF) and type 2 diabetes. *Diabetologia* 50:431–438. <https://doi.org/10.1007/s00125-006-0537-4>
- Leckie RL, Oberlin LE, Voss MW, et al (2014) BDNF mediates improvements in executive function following a 1-year exercise intervention. *Front Hum Neurosci* 8:1–12. <https://doi.org/10.3389/fnhum.2014.00985>
- Levinger I, Goodman C, Matthews V, et al (2008) BDNF, metabolic risk factors, and resistance training in middle-aged individuals. *Med Sci Sport Exerc* 40:535–541. <https://doi.org/10.1249/MSS.0b013e31815dd057>
- Liu-Ambrose T, Nagamatsu LS, Graf P, et al (2010) Resistance training and executive functions: A 12-month randomized controlled trial. *Arch Intern Med* 170:170–178. <https://doi.org/10.1001/archinternmed.2009.494>
- Ma F, Wu T, Miao R, et al (2014) Conversion of mild cognitive impairment to dementia among subjects with diabetes: A population-based study of incidence and risk factors with five years of follow-up. *J Alzheimer's Dis* 43:1441–1449. <https://doi.org/10.3233/JAD-141566>
- Meek TH, Wisse BE, Thaler JP, et al (2013) BDNF action in the brain attenuates diabetic hyperglycemia via insulin-independent inhibition of hepatic glucose production. *Diabetes* 62:1512–1518. <https://doi.org/10.2337/db12-0837>
- Memória CM, Yassuda MS, Nakano EY, Forlenza O V. (2013) Brief screening for mild cognitive impairment: validation of the Brazilian version of the Montreal cognitive assessment. *Int J Geriatr Psychiatry* 28:34–40. <https://doi.org/10.1002/gps.3787>
- Miranda M, Morici JF, Zanoni MB, Bekinschtein P (2019) Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. *Front Cell Neurosci* 13:1–25. <https://doi.org/10.3389/fncel.2019.00363>
- Munshi MN (2017) Cognitive Dysfunction in Older Adults With Diabetes: What a Clinician Needs to Know. *Diabetes Care* 40:461–467. <https://doi.org/10.2337/dc16-1229>
- Nagamatsu LS, Handy TC, Hsu CL, et al (2012) Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment. *Arch Intern Med* 172:666–8.

<https://doi.org/10.1001/archinternmed.2012.379>

Neeper SA, Gómez-Pinilla F, Choi J, Cotman CW (1996) Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Res* 726:49–56.

[https://doi.org/10.1016/0006-8993\(96\)00273-9](https://doi.org/10.1016/0006-8993(96)00273-9)

Palta P, Schneider ALC, Biessels GJ, et al (2014) Magnitude of cognitive dysfunction in adults with type 2 diabetes: A meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains. *J Int Neuropsychol Soc* 20:278–291.

<https://doi.org/10.1017/S1355617713001483>

Pan W, Banks WA, Fasold MB, et al (1998) Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology* 37:1553–1561. [https://doi.org/10.1016/S0028-3908\(98\)00141-5](https://doi.org/10.1016/S0028-3908(98)00141-5)

Paula JJ de, Costa MV, Andrade G de F de, et al (2016) Validity and reliability of a “simplified” version of the Taylor Complex Figure Test for the assessment of older adults with low formal education. *Dement Neuropsychol* 10:52–57. <https://doi.org/10.1590/s1980-57642016dn10100010>

Rasmussen P, Brassard P, Adser H, et al (2009) Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Exp Physiol* 94:1062–1069.

<https://doi.org/10.1113/expphysiol.2009.048512>

Rozanska O, Uruska A, Zozulinska-Ziolkiewicz D (2020) Brain-derived neurotrophic factor and diabetes. *Int J Mol Sci* 21:. <https://doi.org/10.3390/ijms21030841>

Sadanand S, Balachandar R, Bharath S (2016) Memory and executive functions in persons with type 2 diabetes: a meta-analysis. *Diabetes Metab Res Rev* 32:132–142. <https://doi.org/10.1002/dmrr.2664>

Sanders LMJ, Hortobágyi T, Gemert S la B van, et al (2019) Dose-response relationship between exercise and cognitive function in older adults with and without cognitive impairment: A systematic review and meta-analysis. *PLoS One* 14:1–24. <https://doi.org/10.1371/journal.pone.0210036>

Sartorius A, Hellweg R, Litzke J, et al (2009) Correlations and discrepancies between serum and brain tissue levels of neurotrophins after electroconvulsive treatment in rats. *Pharmacopsychiatry* 42:270–276. <https://doi.org/10.1055/s-0029-1224162>

Sharma G, Parihar A, Talaiya T, et al (2020) Cognitive impairments in type 2 diabetes, risk factors and preventive strategies. *J Basic Clin Physiol Pharmacol* 31:. <https://doi.org/10.1515/jbcpp-2019-0105>

Silveira-Rodrigues JG, Pires W, Ferreira Gomes P, et al (2021) Combined exercise training improves specific domains of cognitive functions and metabolic markers in middle-aged and older adults with type 2 diabetes mellitus [Manuscript submitted for publication]. *Diabetes Res Clin Pract* 173:108700. <https://doi.org/10.1016/j.diabres.2021.108700>

Sinclair AJ, Girling AJ, Bayer AJ (2000) Cognitive dysfunction in older subjects with diabetes mellitus: impact on diabetes self-management and use of care services. All Wales Research into Elderly (AWARE) Study. *Diabetes Res Clin Pract* 50:203–12

Squire LR (2004) Memory systems of the brain: A brief history and current perspective. *Neurobiol Learn Mem* 82:171–177. <https://doi.org/10.1016/j.nlm.2004.06.005>

Sun Z, Yu J, Liu Y-L, et al (2018) Reduced Serum Levels of Brain-Derived Neurotrophic Factor Are Related to Mild Cognitive Impairment in Chinese Patients with Type 2 Diabetes Mellitus. *Ann Nutr Metab* 73:271–281. <https://doi.org/10.1159/000493275>

Swift DL, Johannsen NM, Myers VH, et al (2012) The effect of exercise training modality on serum brain derived neurotrophic factor levels in individuals with type 2 diabetes. *PLoS One* 7:1–7. <https://doi.org/10.1371/journal.pone.0042785>

Szuhany KL, Bugatti M, Otto MW (2015) A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *J Psychiatr Res* 60:56–64. <https://doi.org/10.1016/j.jpsychires.2014.10.003>

Tang L, Kang Y, Yin B, Fan X-S (2017) Effects of weight-bearing ladder and aerobic treadmill exercise on learning and memory ability of diabetic rats and its mechanism. *Chinese J Appl Physiol* 33:436–440. <https://doi.org/10.12047/j.cjap.5570.2017.105>

Vedhara K, Wadsworth E, Norman P, et al (2004) Habitual prospective memory in elderly patients with Type 2 diabetes: implications for medication adherence. *Psychol Health Med* 9:17–27. <https://doi.org/10.1080/13548500310001637724>

Voss MW, Erickson KI, Shaurya R, et al (2013) Neurobiological markers of exercise-related brain plasticity in older adults. *Brain Behav Immun* 28:90–99. <https://doi.org/10.1016/j.bbi.2012.10.021>

Walsh JJ, Tschakovsky ME (2018) Exercise and circulating BDNF: Mechanisms of release and implications for the design of exercise interventions. *Appl Physiol Nutr Metab* 43:1095–1104. <https://doi.org/10.1139/apnm-2018-0192>

Zhen YF, Zhang J, Liu XY, et al (2013) Low BDNF is associated with cognitive deficits in patients with type 2 diabetes. *Psychopharmacology (Berl)* 227:93–100. <https://doi.org/10.1007/s00213-012-2942-3>

## Declarations

### Acknowledgments

The authors are thankful to the funding support agencies (FAPEMIG, CNPq). This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – financial code 001. The authors are also thankful to the assistance of Laboratório do Movimento/UFMG,

Laboratório de Imunometabolismo/UFMG, and Laboratório de Fisiologia do Exercício/UFMG members in data collection and exercise training.

## **Funding supports**

This work was funded by the Minas Gerais research support foundation (Fundação de Amparo à Pesquisa de Minas Gerais, FAPEMIG code APQ-00417-15 and code APQ 0354615), Coordination for the Improvement of Higher Education Personnel (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, CAPES) and for Pró-reitoria de Pesquisa da Universidade Federal de Minas Gerais (PRPq-UFMG). This study was also financed by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – financial code 001. The funding agencies had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the report for publication.

## **Competing interests**

The authors declared no potential conflicts of interest.

## **Author contribution (CrediT author statement)**

SILVEIRA-RODRIGUES, JG: Conceptualization, Data Curation, Validation, Formal Analysis, Investigation, Methodology, Project Administration, Software, Writing – Original Draft Preparation and Writing – Review & Editing. MARINHO, NGHM: Conceptualization, Formal Analysis, Validation, Writing – Original Draft Preparation and Writing – Review & Editing. Writing – Review & Editing. FARIA, LO: Conceptualization, Data Curation, Formal Analysis, Validation, Writing – Original Draft Preparation and Writing – Review & Editing, Writing – Review & Editing. PEREIRA, DS: Formal Analysis, Writing – Original Draft Preparation and Writing – Review & Editing. Writing – Review & Editing. SOARES, DD: Data Curation, Conceptualization, Formal Analysis, Validation, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Review & Editing.

## **Data availability**

## Figures

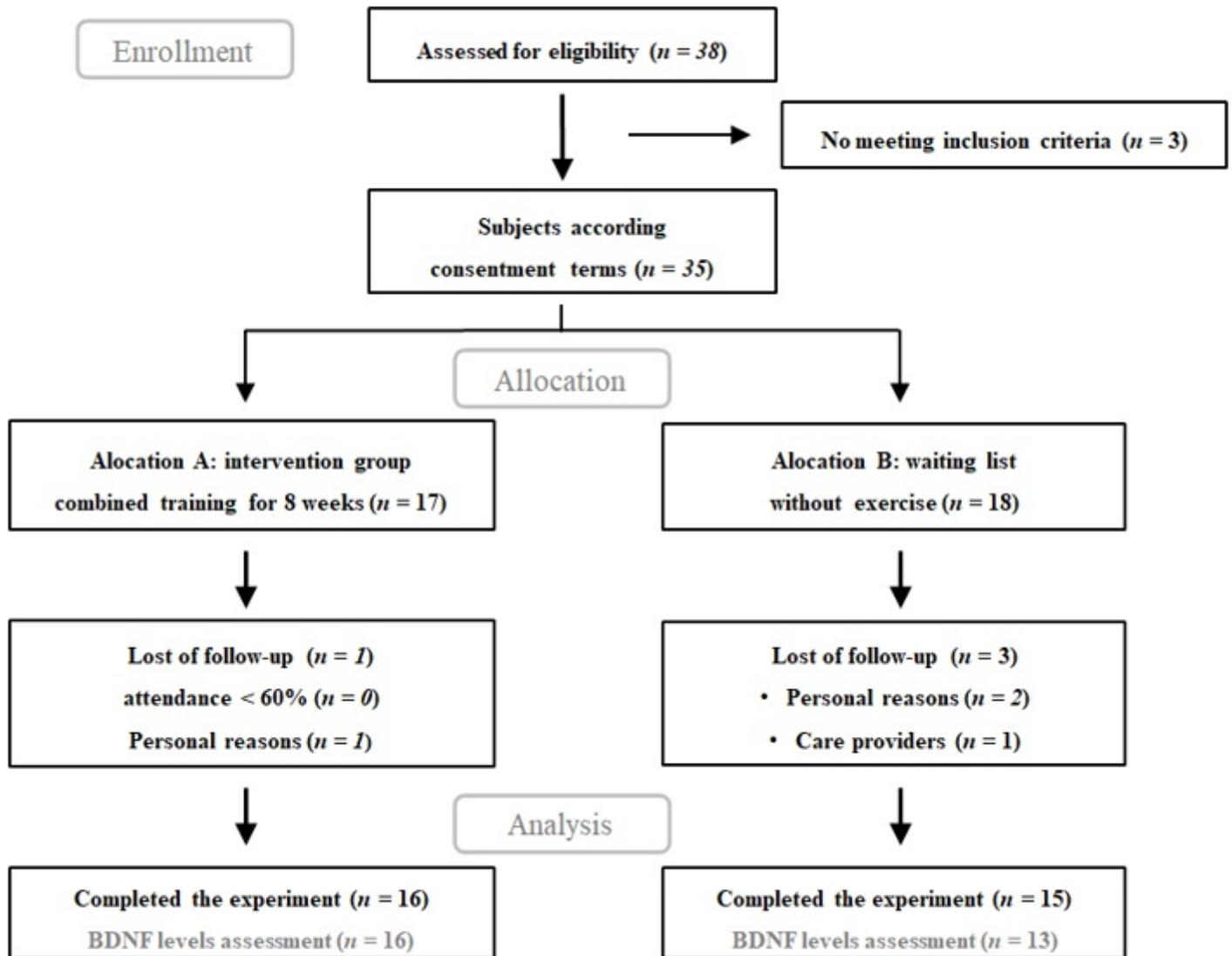


Figure 1

CONSORT Flow Chart

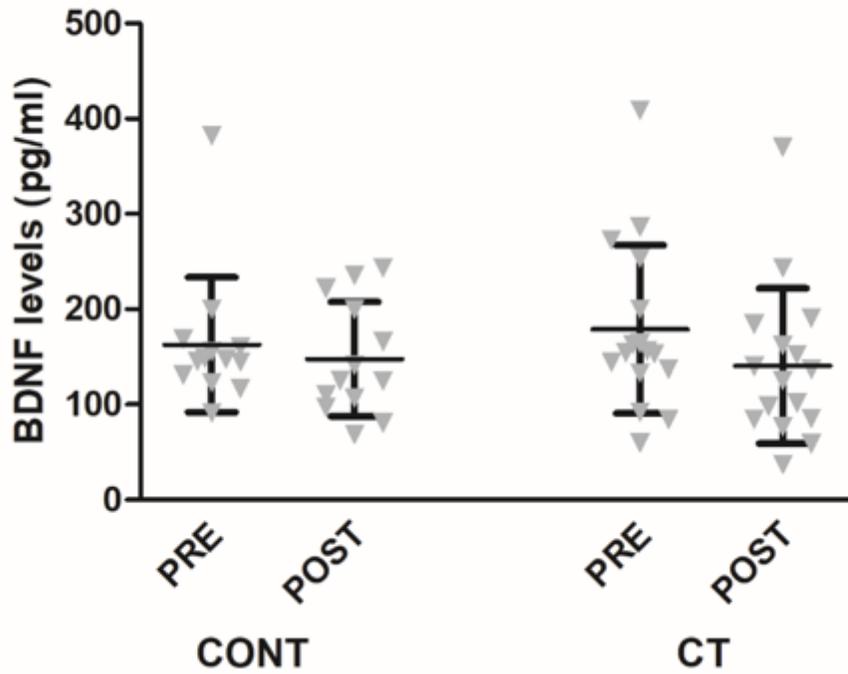


Figure 2

Pre- and post-intervention plasmatic BDNF levels (Combined training group, CT,  $n=16$  and Control group, CONT,  $n=13$ ). Values are mean  $\pm$  SD.

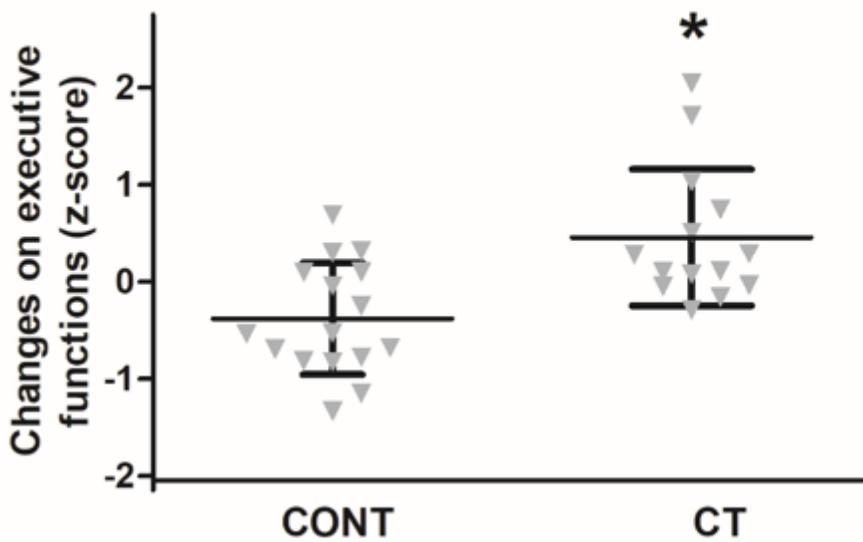


Figure 3

Changes (Post minus Pre) in composite score of executive functions (Combined training group, CT,  $n=16$  and Control group, CONT,  $n=14$ ). Values are mean  $\pm$  SD. \* indicates a significant difference ( $p<0.05$ ) in unpaired *Student's* T-test.

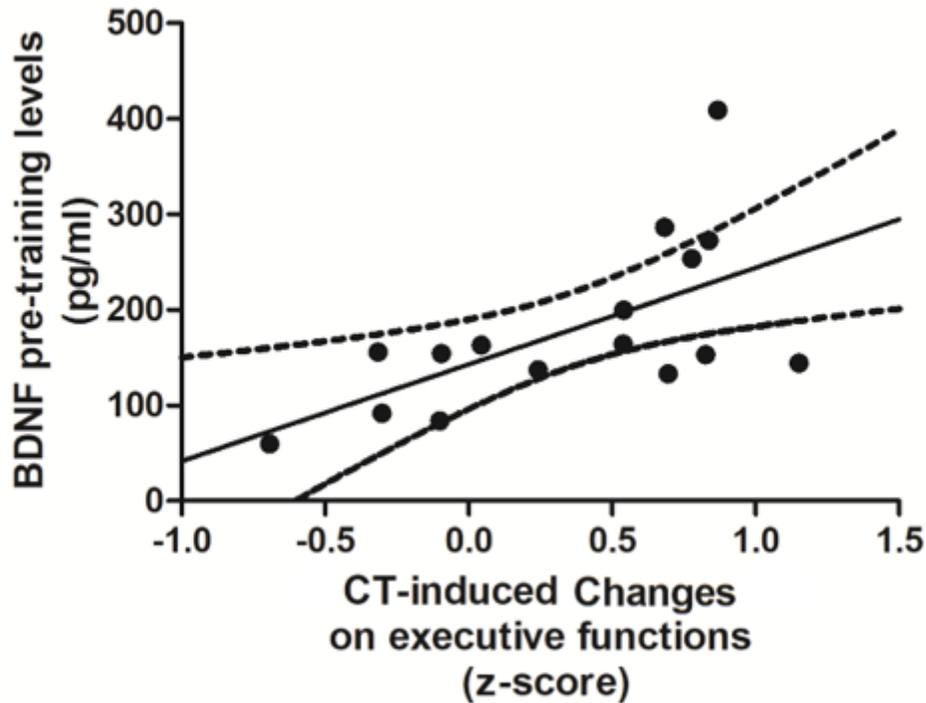


Figure 4

Relationship between pre-training plasma BDNF levels and composite z-score of CT-induced changes on executive functions. Note: dotted line represents the 95% confidence interval. Regression equation: CT-induced changes on executive functions = 0.444 - (0.00461 \* pre-CT resting BDNF levels).

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [OpenData.rar](#)