Astaxanthin Supplementation Preserves Cognitive Markers of Executive Function Following Mental Fatigue in Females

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Research Article

Keywords: Antioxidant, Reaction Time, Brain Health, Dietary Supplement

Posted Date: December 16th, 2025

DOI: https://doi.org/10.21203/rs.3.rs-8196814/v1

Additional Declarations: No competing interests reported.

Abstract

Mental fatigue (MF) is a psychobiological state caused by prolonged periods of demanding cognitive activity, often characterized by impairments to cognitive performance. Astaxanthin (AX) is a naturally occurring antioxidant that can cross the blood-brain barrier and may preserve cognition when presented with a MF challenge. As yet, no studies have yet been conducted in an all-female cohort. This is the first study to investigate 4-weeks of AX supplementation on markers of cognitive performance (reaction time (RT), speed, and responses correct per second (RCS), visual analog scale of mental exertion (VAS-E)) following acute MF. Twenty-five recreationally active female subjects (AX: $n = 13$, PLA: $n = 12$) completed a battery of cognitive tasks (psychomotor vigilance test (PVT), task-switching (TS), and incongruent flanker (IF)) pre-post supplementation with either AX (12 mg/day) or a placebo (PLA). Following supplementation, PLA exhibited no differences on VAS-E or in any task after MF ($p > 0.05$). However, AX significantly improved RT (TS: ~200 ms; IF: ~50 ms), speed (TS: +20%; IF: +11%), and RCS (TS: pre, 1.04 ± 0.25 vs. post, 1.29 ± 0.24 correct·s; IF: pre, 1.79 ± 0.27 vs. post, 1.97 ± 0.29 correct·s)($p < 0.05$), although no differences were observed in the PVT variables ($p > 0.05$). These findings suggest that AX supplementation may preserve executive functions, such as cognitive flexibility and inhibitory control, under conditions of acute MF but may not influence basic attentional processes in college-age females. These findings have implications for populations where MF is known to occur (i.e., athletes and students), and suggest that dietary supplementation with AX may serve as a potent strategy for mitigating MF.

Introduction

Mental fatigue (MF) is a psychobiological state resulting from prolonged cognitive effort and is associated with impairments to cognitive performance subjective feelings of “tiredness” and “lack of energy (Boksem & Tops, 2008; Marcora, et al., 2009). Notably, MF has been shown to negatively impact physical performance, compounding the demands of exercise and competition (Brown, et al., 2020; Sun et al., 2021; Van Cutsem, et al., 2017). The dual regulation system model proposes that high cognitive demand activates both the mental facilitation and inhibition systems, which can eventually lead to MF (Ishii et al., 2014). When mental facilitation is sustained over time, greater effort is required to maintain cognitive performance, increasing susceptibility to MF. Given these challenges, identifying interventions that mitigate the effects of MF on cognitive and physical performance is of interest to athletes, tactical personnel, and individuals engaged in mentally demanding activities.

One potential intervention for mitigating MF-related declines in cognitive function is astaxanthin (AX), a naturally occurring, red-orange pigmented carotenoid with potent antioxidant and neuroprotective properties. Unlike many other dietary antioxidants, AX can cross the blood-brain barrier due to its unique chemical structure, which features both polar and nonpolar regions (Grimmig et al., 2017; Zhang et al., 2014; Fakhri et al., 2019). This allows AX to integrate into the inner and outer phospholipid bilayers of the mitochondria to scavenge intra- and extra-cellular reactive oxygen species and support neuronal function under conditions of metabolic or cognitive stress. Preclinical studies indicate that AX can protect

neurons in the hippocampus and frontal cortex by reducing oxidative stress in the mitochondria (Zhou et al., 2015).

Human studies have demonstrated that AX supplementation may help preserve cognitive performance, as evidenced by improvements in working and short-term memory, processing speed, response time, and mood (Hayashi et al., 2018; Ito et al., 2018; Satoh et al., 2009; Talbott et al., 2019; Zanotto et al,. 2014). However, a key limitation of this body of research is that most studies have been conducted in either a middle-aged or elderly population (≥ 45 years), many of whom had existing cognitive impairments (Ito et al., 2018; Katagiri et al., 2012; Zanotta et al., 2014). Although MF and age-related cognitive decline originate from different mechanisms, both states manifest in similar performance deficits, such as worse decision-making capacity and slower reaction times. While AX has demonstrated an ability to preserve cognitive function in those with pre-existing impairment, its potential to support cognitive function in young, healthy, and active individuals following acute MF remains unexplored.

Lastly, research examining AX and cognitive outcomes in females are largely absent. Although no findings suggest sex-based differences exist in AX metabolism (Wu, et al., 2020), there do appear to be sex-differences and MF, with females reporting less susceptibility to MF than males (Wylie et al., 2022). Neuroimaging findings have revealed a greater resiliency to MF among females in comparison to their male counterparts (Wylie et al., 2022), and between-sex differences favoring females among various cognitive tasks, including working memory and cognitive endurance (Lejbak et al., 2009; Pliatsikas et al., 2020). Additionally, most AX research on cognitive function has focused on individuals ≥ 45 years (Ito et al., 2018; Katagiri et al., 2012; Zanotto et al., 2014), leaving a gap in understanding the effects of AX supplementation in younger populations. To address these gaps, the present study investigated whether 4-weeks of AX supplementation (12 mg/day) could preserve cognitive performance and mood state following a MF protocol in recreationally active, college-age females.

Materials and Methods

Subjects

Twenty-five recreationally active females (mean ± SD; age, 22 ± 3 y; height, 165.7 ± 6.3 cm; body mass, 63.0 ± 6.9 kg; body fat, 27.5 ± 4.1%) were recruited to participate via word of mouth. All procedures were then explained before providing their written and verbal consent to participate. All subjects were classified as tier 1/recreationally active based on the proposed Participant Classification Framework (McKay et al., 2021). To be considered tier 1, subjects must meet the World Health Organization minimum activity guidelines for adults aged 18–32 years, participate in at least 150–300 min of moderate-intensity activity or 75–150 min of vigorous-intensity activity a week, and complete at least two or more days a week of resistance-training (McKay et al., 2021). Additionally, five subjects were taking oral contraceptives (brands: Cryselle, Haley 24, Tri Sprintec, & Vienva), and twenty subjects were naturally menstruating (menstrual cycle length, 25 ± 4 days). This study was clinically registered

(Registration #: NCT06460181) and approved by the university's Institutional Review Board (IRB#: 2024-018) and was in accordance with the Declaration of Helsinki.

Experimental Approach to the Problem

The present study utilized a double-blind, 2-arm parallel study design (AX or placebo (PLA)) to examine the effect of AX on a battery of cognitive tests via touch screen tablet pre-post MF. Before subject recruitment, the required sample size was calculated *a priori* using an effect size in the psychomotor vigilance task (PVT) from previous research (Cohen's $d = 0.3$), which demonstrated a significant improvement in reaction time (ms) following consumption of a high-caffeinated energy drink (Antonio et al., 2019). Using G*Power (version 3.1) and an effect size of 0.40 for within subjects of each arm, expected power of 0.80 (1-β), and an α of $p \leq 0.05$, our power analysis indicated that a sample size of 16 total subjects would be sufficient to demonstrate significant differences for our chosen battery of cognitive tasks, if differences indeed exist. Anticipating a 1:3 dropout rate, we recruited 25 subjects for this study.

Subjects were randomly assigned to either the AX group ($n = 13$) or the PLA group ($n = 12$) and completed four laboratory visits. The first visit involved familiarization with the cognitive software and the battery of cognitive tests (BCT), which are described in detail below. Visits two and three included administration of the BCT both before and after exposure to either an acute MF protocol or a time-matched no mental fatigue (NMF) condition. Following these initial three visits, subjects were randomly assigned—based on their order of recruitment—to receive either AX or PLA supplementation daily for 4-weeks. The final visit (visit four) involved completion of the BCT following the MF protocol, after the four-week supplementation period.

Pre-Trial

All trials took place at the same time of day (± 30 min) for each subject and were each separated by 48 h. Upon arrival for trial 1, a physical activity readiness questionnaire, an exercise history questionnaire, and a menstrual cycle questionnaire were completed. Each subject then had their body mass (Tanita Corporation, Tokyo, Japan), height (Deteco, Webb City, MO, USA), and body fat assessed using bioelectrical impedance analysis (SECA mBCA 514, SECA North America, Chino, CA, USA).

Subjects were given a list of dietary supplements (e.g., multivitamins, creatine, antioxidants, energy drinks, fruit powders, etc.) to refrain from for at least two weeks before testing. A list of AX-rich foods (e.g., salmon, crustaceans, etc.) was provided to avoid during the 4-week supplementation period. Subjects also completed weekly dietary and physical activity logs (using a fitness and nutrition tracking app on their smartphone or computer), refrained from alcohol and caffeine for 24 h, avoided strenuous physical activity for 48 h, and were asked to arrive well-hydrated and well-rested (i.e., ± 30 min of their usual sleep and wake times) before each experimental trial. Subjects verbally confirmed each criterion

prior to completing the battery of cognitive tasks described below. To standardize habitual diet and exercise volume, subjects maintained dietary and physical activity logs before testing and throughout the 4-week intervention. Logs were submitted weekly to the lead investigator. While training was not controlled, exercise volume was monitored, and subjects were instructed to maintain their usual diet and exercise routines during supplementation.

Familiarization and Mental Fatigue

The BCT (Soma Technologies, Lucerne, Switzerland) was adopted from two previous studies our research team conducted examining the effect of a dietary supplement on markers of cognitive performance following a MF protocol in females (Waldman et al., 2023a, 2023b). The test was administered via a touchscreen iPad tablet (10th generation, Apple) and lasted 16 min. Each cognitive task was chosen to measure low- and high-level cognitive processing domains based on proposed definitions (Chang et al., 2012). During visit 1, the investigator briefed all subjects on each task by verbally explaining and demonstrating each task to them. After each subject verbally acknowledged the purpose and instruction of each respective task, the entire BCT familiarization was completed for a total of three times with each series separated by 2 min of passive rest.

During visits 2 and 3, subjects were counterbalanced to complete either the MF or NMF protocol. During the NMF trial, subjects watched a 20-min video titled “World Class Trains—The Venice Simplon Orient Express” (Pegasus-Eagle Rock Entertainment, 2004). This documentary was chosen due to its incorporation in prior MF investigations (Marcora et al., 2009; Martin et al., 2015; Waldman et al., 2023a) and has been shown to maintain a neutral mood and stable heart rate during viewing (Silvestrini & Gendolla, 2007).

The MF protocol was a 20-min time load dual back (TLDB) task which is known to be an effective protocol for inducing MF in prior investigations (Mortimer, et al., 2024; O’Keeffe, et al., 2019; Staiano, et al., 2024). During the TLDB, subjects were presented with a series of numbers and letters with three labels at the bottom of the screen (the word “Left”, the number “1” or the number “2”). When the letter that was displayed was the same as the previously displayed letter, the subject would press the left button at the bottom of the screen. When an odd number was presented, subjects were to tap the button label “1” and when an even number was presented, subjects were to tap the button label “2” as fast as possible. The task operated in an adaptive mode whereby task difficulty varied with performance to maintain a heightened cognitive load. Upon an incorrect or no response, an audible adverse buzzer would emit from the tablet. Upon finishing either the NMF or MF protocol, subjects then completed a visual analog scale to measure perceptions of MF (VAS-F, 0 mm = “no mental fatigue” to 150 mm = “extreme mental fatigue”) and mental exertion (VAS-E, 0 mm = “no mental exertion” to 150 mm = “extreme mental exertion”).

The purpose of visits 2 and 3 were to confirm that the MF protocol did indeed acutely impair cognitive responses in our female subjects compared to NMF (defined as a significant increase in reaction time

compared to NMF). Following these visits and prior to group randomization, a paired *t*-test was performed on reaction time (ms) in the PVT and VAS-F between the NMF and MF protocols for all of our subjects. Results indicated that MF significantly increased reaction time compared to NMF (~ 2%; p = 0.02). Similarly, MF resulted in a higher VAS-F score (79 ± 37 mm) compared to NMF (39 ± 27 mm) (p = 0.04). Following confirmation of MF (i.e., longer reaction time and higher subjective reporting of MF), all variables of interest (reaction time, speed, and responses correct per second) collected during the pre-supplementation MF visit then served as a baseline for comparing post-supplementation values (POST) during later analysis.

Cognitive Test Battery

The BCT was completed in the same order for each trial. The tablet was placed ~ 1 m away from each subject on a table and subjects were instructed to place their dominant index finger on a legend ~ 15 cm from the screen and return it after each response. Subjects were placed in a quiet and dimly-lit room while being monitored by an investigator through a double-sided window during testing. Three metrics were collected from the battery of cognitive tasks to be used for statistical analysis: (1) reaction time (ms; RT), (2) speed, defined as (Mean $_{\text{step N1}}$/response time) and also known as reciprocal response time, (3) and responses correct per second (RCS).

The first cognitive task completed was a 5-min PVT. The PVT measures sustained low-level cognitive processing by assessing the subject's attention and consistently responding to a visual stimulus. The PVT provided the subjects with a visual stimulus in the form of a circle that appeared in the middle of the screen. The stimulus was presented intermittently for 500 ms or until a response was given.

Following the PVT, subjects completed a 3-min task-switching (TS) test. This task measures the subject's ability to switch between different tasks and represents high-level cognitive processing (also known as cognitive flexibility). Numbers 0–10 were shown to the subjects in either white or red colored font. For white numbers 0–5 and red odd numbers, subjects were instructed to tap a left-facing arrow displayed at the bottom left-hand corner. For white numbers 6–10 and red even numbers, subjects were instructed to tap a right-facing arrow displayed at the bottom right-hand corner. If subjects responded incorrectly or failed to respond in the allotted time, an audible adverse buzzer would emit from the tablet.

The third task was a 3-min incongruent flaker (IF) design to test inhibition. This task assessed the subject's ability to ignore task-irrelevant information and represented high-level cognitive processing. Subjects were presented with a series of five arrows, with four of the five arrows pointing in either the left or the right direction. Subjects were instructed to focus on the middle arrow when it appeared and ignore the two arrows immediately to the left and right of it. Whichever direction the middle arrow was pointing, subjects were to tap at the bottom left- or right-hand corner of the screen, the arrow that corresponded with the middle arrow's respective direction. When incorrect responses occurred, or a response was not given, an audible adverse buzzer would emit from the tablet.

Supplementation Schedule

Following visit 3, subjects were assigned either AX or a PLA and supplemented for 4-weeks at a dose of 12 mg/day. The AX (AX combined with sunflower oil) and a matched PLA (sunflower oil only) capsules were provided by AstaReal (AstaReal, Inc., Moses Lake, WA, USA). An independent investigator labeled the pill bottles “A” or “B”, counted them, and distributed them to the subjects. Each capsule contained 12 mg of either AX or sunflower oil only, and subjects were instructed to ingest one capsule daily with a meal containing a dietary fat source. If a capsule was missed, the subject ingested the missed capsule as soon as possible. Each subject was provided with an undisclosed but previously counted number of capsules in each bottle. Compliance ([capsules ingested]/N ×100) was evaluated once the remaining capsules were returned following the conclusion of all testing. A compliance of less than 90% was considered unacceptable, resulting in the subject's removal. However, all subjects had acceptable compliance; therefore, no subjects were removed from the study prior to statistical analysis.

Statistical Analyses

Data are presented as the mean ± SD with an *a priori* alpha level of $\alpha \leq 0.05$ used to determine significance in all analyses. Provided the primary interest was whether AX mitigated MF following supplementation (baseline vs. POST) and not whether group differences existed, we chose to analyze all primary variables (RT, speed, RCS) for each cognitive task (PVT, IF, TS) and VAS-E with a paired *t*-test for baseline to POST changes *within* groups. Effect sizes were calculated and reported as Cohen’s *d* (*d*: trivial = 0–0.19, small effect = 0.20–0.49, moderate effect = 0.50–0.79, and large effect = ≥ 0.80) in instances where significance occurred. IBM SPSS Statistics v. 27 was used for all statistical analyses.

Results

Pre to post-supplementation, the AX group reported a significantly lower VAS-E (pre, 75.0 ± 30.1 vs. post, 52.6 ± 32.2; $p = 0.006$, $d = 0.95$) while PLA showed no significant differences (pre, 75.7 ± 37.7 vs. post, 64.9 ± 26.8; $p = 0.15$, $d = 0.31$). For all PVT variables, no significant differences were found for either group ($p > 0.05$). For IF, no significant differences were found in the PLA group for all variables ($p > 0.05$). However, improvements were found from AX supplementation identified as a significant decrease in RT ($p = 0.012$, $d = 0.62$), a significant increase in speed ($p = 0.012$, $d = 1.00$) and a significant increase in RCS ($p = 0.013$, $d = 0.67$). For TS, no significant differences were found in the PLA group for all variables ($p > 0.05$). Similar to the IF however, the AX group experienced significant improvements following supplementation identified as a significant decrease in RT ($p = 0.001$, $d = 1.04$), a significant increase in speed ($p = 0.001$, $d = 0.93$), and a significant increase in RCS ($p < 0.001$, $d = 1.06$). RT and RCS can be viewed in Table 1 and speed can be viewed in Figure 1-3.

>>>Insert Figures 1-3. Here

>>>Insert Table 1. Here

Discussion

The primary finding of this study were 4 weeks of AX supplementation (12 mg/day) was effective in preserving executive functions, such as cognitive flexibility and inhibitory control, under conditions of MF, but may not influence basic attentional processes in healthy, female young adults (Table 1). Aside from improvements in higher-domains of cognition following AX supplementation, it appears that AX also lowered subjective reporting of mental exertion as identified by the significantly lower VAS-E. These findings contrast the PLA group, where no significant differences were found for any of the collected variables following the supplementation period.

The study employed a battery of cognitive tasks, including the PVT, TS, and IF tests, to assess the effects of AX on both low- and high-level cognitive processing domains. The results demonstrated that AX supplementation improved speed in high-level cognitive tasks, specifically TS (+ 20%) and IF (+ 11%) (see Figs. 2 and 3), as well as faster RT and higher RCS (Table 1). However, AX did not influence performance in the PVT (Fig. 1 and Table 1), a low-level cognitive task. These findings suggest that AX may be particularly effective in preserving executive functions, such as cognitive flexibility and inhibitory control, under conditions of MF, but may not influence basic attentional processes in females.

The current findings align with previous research demonstrating AX's neuroprotective and cognitive-enhancing properties, particularly in populations with pre-existing cognitive impairments or older adults (Hayashi et al., 2018; Ito et al., 2018; Satoh et al., 2009; Talbott et al., 2019; Zanotta et al., 2014). However, this study extends the literature by demonstrating AX's efficacy in a younger, healthy, and active population, specifically in mitigating MF-related declines in executive function. Notably, the lack of effect on PVT performance contrasts with some prior studies that reported improvements in RT following AX supplementation (Satoh et al., 2009). This discrepancy may be attributed to differences in the cognitive demands of the tasks used, as PVT primarily assesses sustained attention, a low-level cognitive process that may be less sensitive to AX's antioxidant and neuroprotective effects compared to high-level executive functions like task-switching and inhibitory control.

Although our team did not collect mechanistic data, it is possible that AX ability to improve performance in the TS and IF tasks can be explained by its potent antioxidant properties and its unique capacity to cross the blood-brain barrier. During periods of prolonged cognitive effort, MF arises and is characterized by increased subjective feelings of tiredness, reduced cognitive performance, and impaired executive function (Boksem & Tops, 2008). Key mechanisms contributing to MF include the accumulation of reactive oxygen species and oxidative stress in the brain, particularly in regions like the prefrontal cortex and hippocampus, which are critical for high-level cognitive processes (Carillon et al., 2014). AX supplementation may counter the effects of MF however, by integrating into mitochondrial membranes, specifically in the prefrontal cortex and hippocampus (Zhou et al., 2015; Grimmig et al., 2017), which is important provided higher domains of cognition, such as cognitive control, occur in the prefrontal cortex (Pontifex et al., 2019). AX supplementation may also have preserved neuronal efficiency and synaptic plasticity, thereby enhancing cognitive flexibility (TS) and inhibitory control (IF). Interestingly, the lack of

effect observed in the PVT may be due to the task's reliance on basic attentional processes, which are less dependent on the prefrontal cortex and more on subcortical structures like the thalamus and brainstem. These regions may be less susceptible to oxidative stress during MF or may require higher doses or longer supplementation periods for AX to exert measurable effects. These are areas that will require future research. Additionally, the PVT low cognitive demand may not have sufficiently challenged the cognitive system to reveal a benefit of AX supplementation if one existed, whereas the more complex TS and IF tasks likely provide a more sensitive measure of AX.

Several limitations should be acknowledged. First, the groups were not stratified prior to supplementation. Although subjects were randomized to groups, lack of stratification, such as stratification using baseline RT (ms), may have introduced baseline group differences which could skew findings in favor of the AX group. Future research can control for this limitation by stratifying subjects to groups based on cognitive performance in the task of primary interest (e.g., PVT). Second, the 4-week supplementation period may have been insufficient to reveal any effect from AX supplementation for low-level cognitive tasks like the PVT. Longer intervention periods or higher doses may be necessary to observe effects on basic attentional processes.

In conclusion, our study provides evidence that 4 weeks of AX supplementation can mitigate MF-related declines in high-level cognitive performance, specifically in tasks requiring cognitive flexibility and inhibitory control. These findings are similar to those reported in older adults (Hayashi, et al., 2018; Katagiri et al., 2012; Queen, et al., 2024) but have not been demonstrated in their younger counterparts until the present study. These findings highlight AX's potential as a dietary intervention to support cognitive resilience under conditions of prolonged mental effort. However, the lack of effect on PVT performance suggests that AX's benefits may be task-specific, with greater efficacy in complex cognitive tasks compared to basic attentional processes. Future research should explore AX's effects in diverse populations, including males and older adults, and investigate the impact of longer supplementation periods or higher doses on both low- and high-level cognitive functions.

Declarations

Funding:

This study was funded by Astareal Inc. The astaxanthin and matched placebo were provided by Asatreal Inc. Funding was used only for the compensation of subjects for their participation.

Conflicts of Interest:

The authors declare no conflict of interest.

Ethics approval and consent to participate:

All study activities were approved by the University of North Alabama's institutional review board. All participants gave informed consent.

Availability of data and materials:

All data and materials will be made available upon request.

Author Contributions:

GB and HW conceptualized the present study. All authors contributed to the methodology. GB, EO, and HW completed the formal analysis. GB completed the investigation and data curation. HW completed project supervision. GB and HW completed writing of the original draft, and all authors contributed to the review and editing process, along with approval of the final submitted paper.

Acknowledgments:

The authors thank those who participated in this study and those who helped with the collection of data, including Ashlyn DeArman, Lynnsey Bowling, Noah Bishop, Courtney Dillard, Katherine McAdams, Natalie Byron, Daylee Scudder, and German Roca. The authors would like to thank SOMA Technologies for the use of their cognitive testing software and Grant Hayes for his input on cognitive testing methods. The authors also would like to thank AstaReal Inc., for their donation of the supplements and Karen Hecht for her input on the dosage protocol implemented.

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Table

Table 1. Measures of cognitive performance (mean ± SD) for astaxanthin (n = 13) and placebo (n = 12). Effect sizes were calculated and reported as Cohen's *d*.

	Reaction Time			RCS		
	Baseline	*Post*	*Effect Size*	*Baseline*	*Post*	*Effect Size*
PVT						
Astaxanthin	402.7 ± 49.9	426.4 ± 42.4	0.35	2.5 ± 0.34	2.17 ± 0.48	0.55
Placebo	400.0 ± 51.7	406.6 ± 83.1	0.08	2.5 ± 0.35	2.3 ± 0.27	0.63
Task Switch						
Astaxanthin	937.2 ± 198.6	760.9 ± 136.4*	0.29	1.05 ± 0.25	1.29 ± 0.24*	0.41
Placebo	948.0 ± 214.7	830.6 ± 354.9	1.14	1.06 ± 0.27	1.16 ± 0.32	1.27
Incongruent Flanker						
Astaxanthin	567.4 ± 98.6	512.1 ± 77.7*	0.79	1.79 ± 0.31	1.85 ± 0.31*	0.77
Placebo	570.3 ± 107.8	545.4 ± 87.9	0.23	1.79 ± 0.27	1.97 ± 0.29	0.18

* Significantly different ($p < 0.05$) from respective baseline. RCS = responses correct per second.

Figures

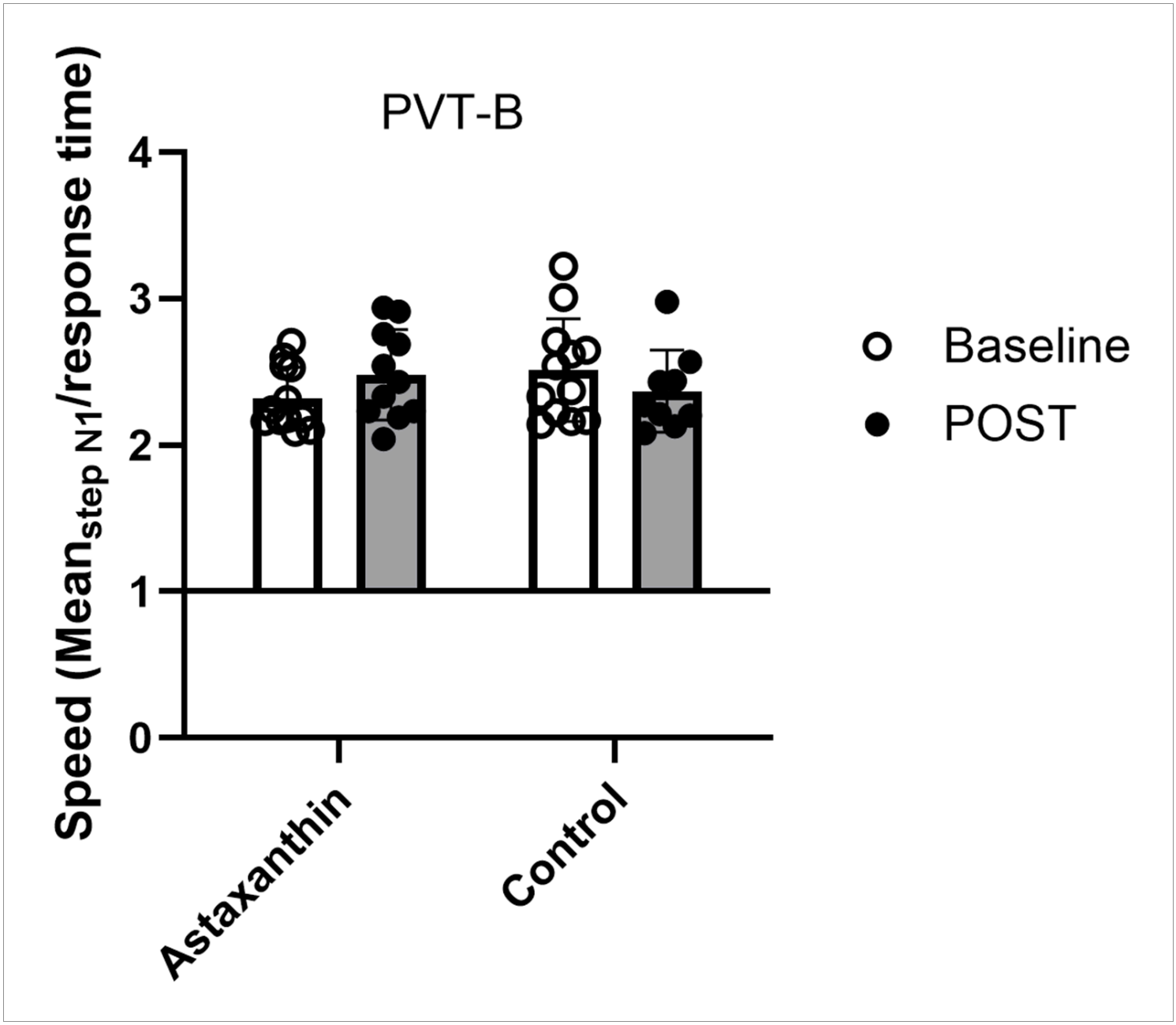

Figure 1

Pairwise comparisons of individual differences between timepoints (baseline vs. post-supplementation) for astaxanthin and PLA speed in the PVT. *Clear* circles represent baseline and *filled* circles represent post-supplementation. Data presented as mean ± SD values.

* = $p < 0.05$.

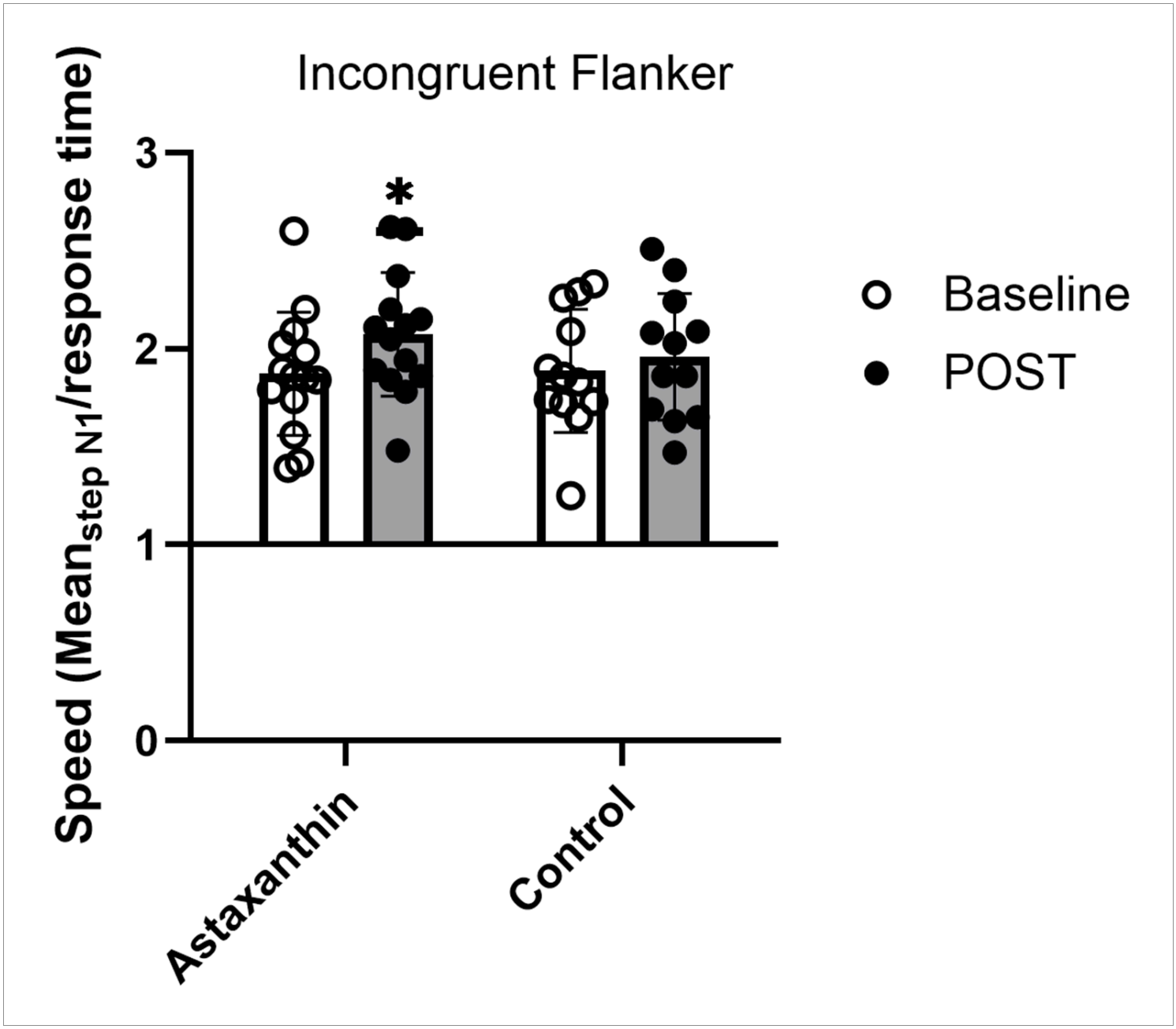

Figure 2

Pairwise comparisons of individual differences between timepoints (baseline vs. post-supplementation) for astaxanthin and PLA speed in the incongruent flanker. *Clear*circles represent baseline and *filled*circles represent post-supplementation. Data presented as mean ± SD values.

* = $p < 0.05$.

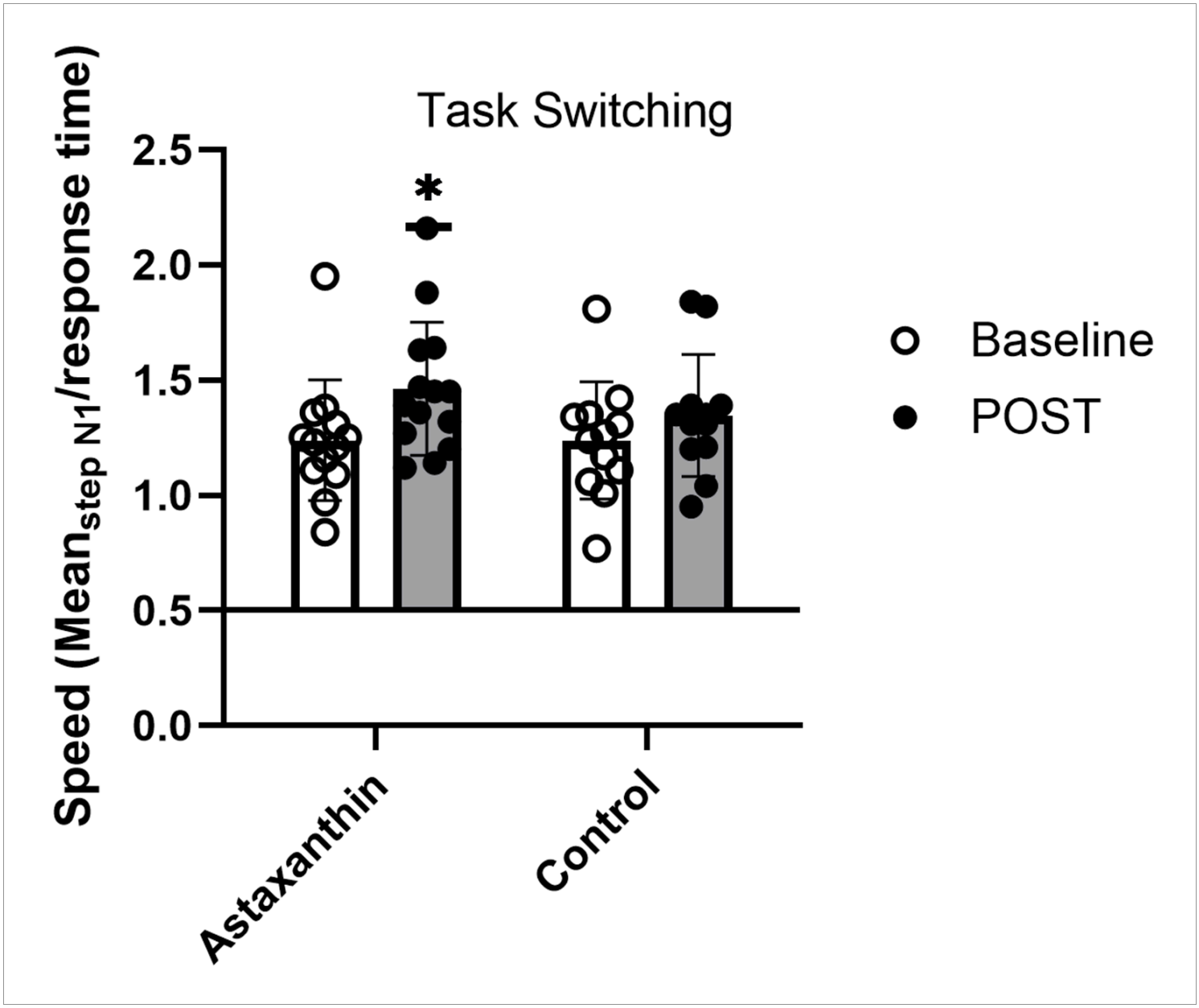

Figure 3

Pairwise comparisons of individual differences between timepoints (baseline vs. post-supplementation) for astaxanthin and PLA speed in the task switch. *Clear* circles represent baseline and *filled* circles represent post-supplementation. Data presented as mean ± SD values.

* = $p < 0.05$.