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Novel Energy Drink Improves Cognitive Function and Mood, without Influencing Myocardial Oxygen Demand or Ventricular Repolarization in Adult Gamers: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

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ABSTRACT

There are limited available data assessing the efficacy of acute energy drink consumption on cognition and gaming performance, nor on cardiovascular safety.

Objectives: To examine the efficacy of acute consumption of a novel energy drink (C4S) versus placebo for improving cognitive and gaming performance and mood. Secondarily, we examined the cardiovascular safety profile of acute C4S consumption.

Methods: Forty-five healthy, young adult video gamers completed two experimental visits in randomized order where they consumed either C4S or a placebo and then completed a validated battery of neurocognitive tests, played five video games, and completed a mood state survey. Blood pressure (BP), heart rate (HR), oxygen saturation, and electrocardiogram measurements were taken at baseline and repeated throughout each visit.

Results: Acute consumption of C4S improved cognitive flexibility (absolute mean or median difference [95% CI] = +4.3 [2.2–6.4]; $p < 0.001$; $d = 0.63$), executive function (+4.3 [2.3–6.3]; $p < 0.001$; $d = 0.63$), sustained attention (+2.1 [0.6–3.6]; $p = 0.01$; $d = 0.44$), motor speed (+2.9 [0.8–4.9]; $p < 0.001$; $d = 0.44$), psychomotor speed (+3.9 [0.1–7.7]; $p = 0.04$; $d = 0.32$) working memory (+1.0 [0.1–1.9]; $p = 0.02$; $d = 0.35$), and performance in the two-dimensional visuospatial game Tetris (+463 [-419–2,065] pts; $p = 0.049$; $d = 0.30$) compared to placebo. C4S also improved Fatigue-Inertia (-1 [-3–0]; $p = 0.004$; $d = 0.45$), Vigor-Activity (+2.4 [1.3–3.6]; $p < 0.001$; $d = 0.64$), Friendliness (+0 [0–1]; $p = 0.04$; $d = 0.32$), and Total Mood Disturbance (-3 [-6–0]; $p = 0.002$; $d = 0.44$). BP increased slightly in C4S versus placebo, while HR decreased from baseline to post-drink in the C4S condition. Rate-pressure-product was higher in C4S versus placebo independent of time but did not increase from baseline. There was no effect on corrected QT interval.

Conclusion: Acute consumption of C4S was efficacious for cognitive performance, visuospatial gaming performance, and mood enhancement, and had no effect on myocardial oxygen demand or ventricular repolarization, despite being associated with increases in BP.

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Introduction

The United States energy drink industry has grown exponentially since being introduced to the market in 1997 (1). Between 2005 and 2025, revenue from energy drink sales in the United States is projected to increase six-fold (2). Two of the most commonly reported reasons for use of energy drinks by consumers are to promote wakefulness and increase energy (3). Thus, a primary factor for the dramatic increases in energy drink consumption is likely the cultural valuation placed on productivity and performance.

Productivity in modern work and education is associated with cognitive performance and mood (4–7). Cognitive enhancers, also called nootropics, are a chemically diverse class of compounds reported to improve various aspects of mental processes (e.g., cognitive function) including memory, cognitive flexibility, concentration, and attention (8, 9). Consumption of cognitive enhancers by healthy individuals has increased alongside the general population's growing desire to enhance productivity and performance, or to gain a competitive edge by supporting cognitive function and mood (10–14). Consequently, many dietary supplement companies now incorporate natural nootropics in products marketed to improve cognitive function (14, 15). Energy drink manufacturers are a major contributor to this trend, creating novel formulations advertised to improve mental function (16).

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E-sports players (i.e., "video gamers") are a significant target market for these novel energy drink formulations (17, 18). Electronic sports, including video games and e-games, are among the fastest growing entertainment industries in America. In fact, 66% of the U.S. population aged 13 years and older reported playing video games regularly in 2018 (19). According to the Entertainment Software Association, the greatest proportion of video game users is among adults ages 18 – 54 years (e.g., 64% of all video gamers) and recent market projections indicate that the worldwide number of video gamers will surpass three billion by 2023 (20). Increasing complexity and competition associated with gaming (21–23) has led gamers to seek cognition-enhancing products in an effort to increase gaming performance. While there is concern over the abuse of prescription cognitive enhancers amongst professional gamers (24), many recreational and semi-competitive gamers seek less controversial over-the-counter products to gain an edge. Energy drink companies have thus also increasingly targeted advertising and sponsorship toward the video gaming population (17).

Despite a substantial body of literature examining the efficacy of cognitive enhancers for populations with neurodegenerative or psychological disorders (11, 25–28), there are few available data supporting the efficacy and safety of finished product (e.g., ready-to-drink) energy drink formulations that are marketed to improve cognitive performance in otherwise healthy individuals (13, 14, 29, 30). A few studies have examined the effects of caffeine in combination with glucose (16) or cognitive enhancers such as citicoline (or, CDP-choline) (31) on cognitive performance. However, several of these studies are limited by a lack of neuropsychological testing (32) and between-subjects designs (31). Further, although data regarding the cardiovascular safety of acute energy drink consumption are equivocal (33–36), there are multiple reports indicating that energy drink consumption may produce potentially dangerous arrythmias, especially if consumed in high volumes (37, 38). Therefore, we conducted a randomized, double-blind, placebo-controlled crossover trial in 45 young adult gamers to examine the efficacy and safety of acute consumption of a non-caloric, novel energy drink formulation (C4 Smart Energy™ (C4S)) containing 200 mg of naturally derived caffeine (extracted from green tea) in combination with citicoline, niacin and vitamin B-12, and N-Acetyl-L-Tyrosine. We hypothesized that the novel energy drink would improve cognitive function and gaming performance, while increasing blood pressure, heart rate, and myocardial oxygen demand, without impacting ventricular repolarization.

Materials and methods

Participants

Two-hundred and thirty individuals provided informed consent and completed online screening for this study (Figure 1). Of these, 67 were determined to be eligible for participation and 65 agreed to participate. Of those who agreed to participate, 20 did not complete the study. The reasons provided for not completing the study included: unexpected events ($n = 8$), insufficient time ($n = 4$), scheduling conflicts ($n = 3$), lost to follow-up ($n = 2$), unspecified ($n = 2$), and noncompliance with the study protocol ($n = 1$). Therefore, 45 total participants (37 M; 8 F) completed the study. The characteristics of these participants are presented in Table 1.

Participants were recruited *via* recruitment emails distributed through the university mass-email system, flyers placed on campus and in the community, and by word of mouth. Prior to enrollment, participants completed an

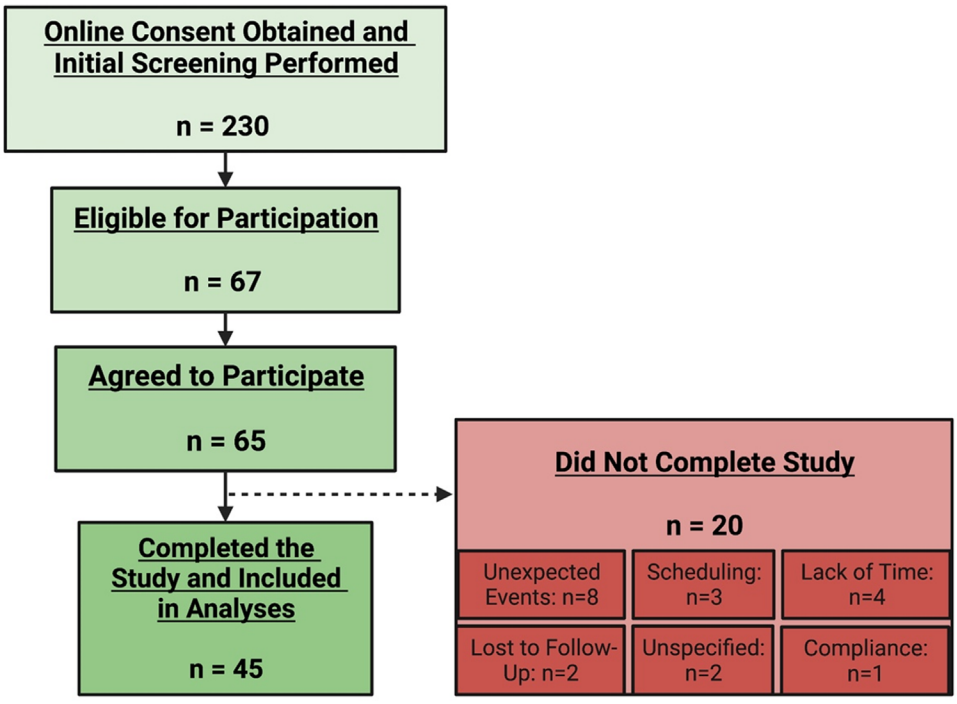

Figure 1. Flow-chart illustrating participant enrollment and completion.

Table 1. Demographic characteristics of sample ($n = 45$).

Characteristic	Mean	SD	Frequency (n)	Relative Frequency (%)
Age (yr)	25.2	5.8	–	–
Height (in)	68.2	3.5	–	–
Weight (lb)	169	34	–	–
Weight (kg)	76.7	15.4	–	–
BMI	25.5	4.4	–	–
Caffeine Intake, mg/day	61.7	67.1	–	–
Caffeine Intake, mg/kg body weight/day	0.8	0.9	–	–
Sex				
Female	–	–	8	18%
Male	–	–	37	82%
Race*				
White	–	–	17	47.2%
Asian	–	–	10	27.8%
Hispanic/Latino	–	–	3	8.3%
Bi-racial	–	–	3	8.3%
Black	–	–	1	2.7%
American Indian/ Alaskan Native	–	–	1	2.7%
Other	–	–	1	2.7%
Ethnicity*				
Hispanic/Latino	–	–	4	11.1%
Not Hispanic/ Latino	–	–	32	88.9%

*Indicates race/ethnicity data only available in 36 participants.

informed consent document and health and lifestyle behavior questionnaires. In order to qualify, participants must have been between the ages of 20 and 50 years (inclusive), played video games for more than 1 h per week, engaged in physical activity at least three times per week, consumed less than 21 servings of caffeinated beverages per week, been a non-user of nicotine and cannabis, and could not have been a current competitive athlete. In addition, participants were excluded if they had a body mass index (BMI) greater than 35 kg/m^2, a preexisting heart condition, high blood pressure, metabolic syndrome, attention deficit hyperactivity disorder (ADHD), clinical depression or other mental health condition, history of chronic (> 6 months) drugs or alcohol abuse, digestive disorder or sensitivity, or an allergy to any of the ingredients contained in the novel energy drink or placebo beverage. This study complied with the Declaration of Helsinki and was approved by and carried out in accordance with the University's Institutional Review Board for the protection of human subjects (IRB # 202108063; Approval Date: 09/17/2021).

Experimental design

This trial utilized a randomized, double-blind, placebo-controlled crossover design involving two experimental visits that were completed at the same time of day (±1 h) and separated by a 7.1 ± 0.5-day washout period. Each participant underwent familiarization 6.9 ± 2.6 days prior to the first experimental visit to become habituated to the cognitive test instructions, gaming platforms and video games, and the timing and order of tasks. Prior to arrival at each experimental visit, participants abstained from alcohol for 72 h, all planned exercise for 48 h, and caffeine for 24 h, and arrived at the laboratory in a fasted (5-10 h) state.

Upon arrival for each experimental visit, participants provided a urine sample to verify hydration status *via* hand-held refractometry (Fisherbrand, Pittsburgh, PA, USA). Study visits commenced only upon verification that the participant was not experiencing severe dehydration, which was defined as a urine specific gravity (USG) of 1.030 and above. The average USGs at the experimental versus placebo-assigned visits were 1.013 ± 0.0076 and 1.013 ± 0.0077, respectively, and were not different ($p = 0.82$). Following a 10-minute rest period, baseline cardiovascular measurements (e.g., blood pressure, oxygen saturation, heart rate, and cardiac electrical activity) were performed. The participant then consumed the test beverage and underwent a 40-minute waiting period. Cognitive stimulation was minimized and standardized during this period by prohibiting the use of phones or computers, reading, and writing. Instead, participants were given picture books containing landscape photography to prevent severe boredom and to standardize the stimulus. Immediately after the waiting period, cardiovascular measurements were again taken. The participant then completed the cognitive test battery and played five different video games. Cardiovascular measurements were repeated immediately following completion of the final video game. Participants then completed questionnaires to assess adverse events and mood state during the period following test beverage consumption. The order of test beverage consumption (C4S or PLA) at experimental visits 1 and 2 was randomized for each participant. Following the completion of experimental visit 2, participants also completed a brief questionnaire to assess blinding efficacy. Prior to experimental visits 1 and 2, participants completed written food, physical activity, and sleep logs to control for lifestyle factors. A visualization of the visit timeline is provided in Figure 2.

Lifestyle controls

Participants tracked their nutrition, physical activity, and sleep during the week preceding each experimental visit. Participants completed a 3-day dietary log (39, 40) to track all food, drink, and supplement consumption on two weekdays and one weekend day, including the day immediately preceding their experimental visit. These data were entered into ESHA Food and Nutrition Database (ESHA Research, Oak Brook, IL, USA), which provided calculations of nutritional intake including: total energy (kcals/day), protein (g/day), fat (g/day), carbohydrates (g/day) and caffeine (mg/day) which were analyzed as both absolute and relative (to bodyweight) values. Physical activity and sleep were logged on all seven days during the preceding week using the Centers for Disease Control and Prevention (CDC) My Physical Activity Diary and the Sleep Foundation Sleep Log, respectively. Data collected from the physical activity logs included exercise description, duration, and effort level (low, moderate, high). The recorded physical activities were then converted to Metabolic Equivalent of Task (MET) values

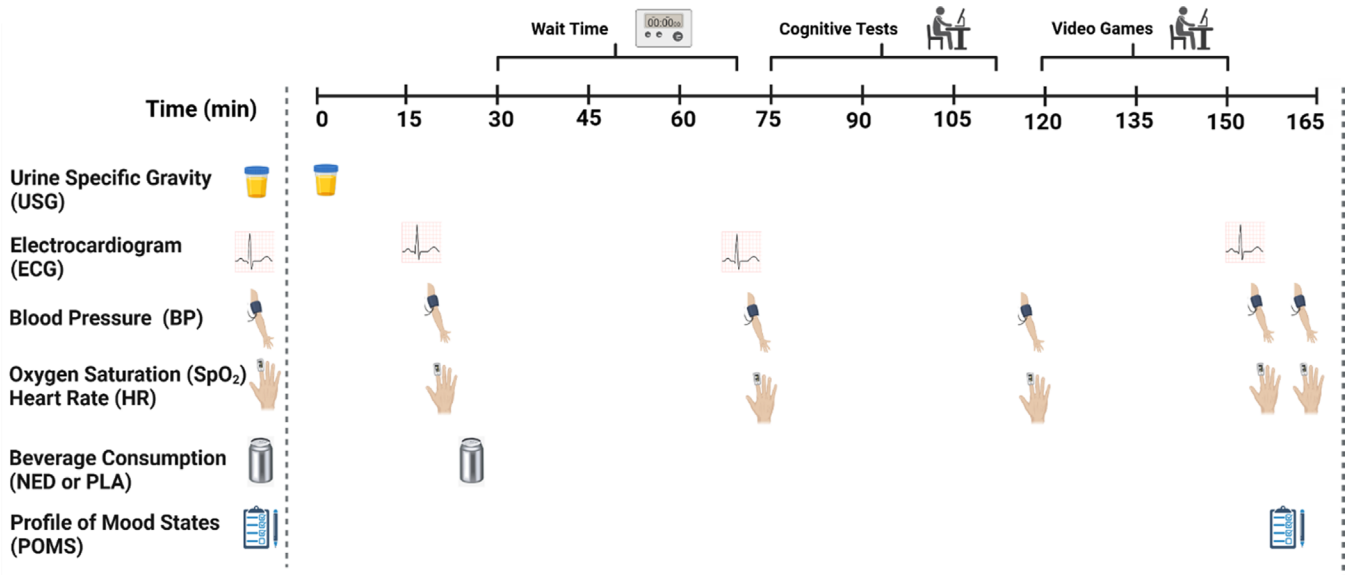

Figure 2. Illustration of the experimental visit timeline. Created using BioRender.com.

using the 2011 Compendium of Physical Activities. Weekly physical activity was assessed by calculating MET·min/week of physical activity (PA). Data collected from the sleep logs included evening (after 6:00pm) consumption of caffeine, nicotine, alcohol, total hours slept per night, frequency of sleep disruptions (disruptions/night), and subjective ratings of sleep quality on a scale from 1 (poor sleep) to 5 (great sleep).

Energy drink and placebo

The novel energy drink treatment for this study was C4S (Nutrabolt®, Woodbolt Distribution LLC, Austin, TX, USA). Participants were given five minutes to consume 16 oz of either the C4S or placebo beverage (PLA) at each experimental visit. The PLA was matched to C4S for volume, appearance, taste, aroma, packaging, and mouthfeel, but was devoid of any active ingredients. Thus, both C4S and PLA contained equivalent energy (Calories), malic acid, citric acid, and inactive ingredients such as sucralose and natural flavoring. The active ingredients in C4S included: 200 mg caffeine (from InnovaTea® Green Tea (leaf) extract (NutriScience® Innovations, LLC, Milford, CT, USA), Citicoline/CDP-Choline (Cognizin®, Kyowa Hakko USA, Inc., New York, NY, USA) at a dose previously demonstrated to be efficacious when administered acutely (31, 32), Niacin (as Niacinamide), Tyrosine (as N-Acetyl-L-Tyrosine), and Vitamin B12 (as Cyanocobalamin). The Nutrition Facts panel and ingredient list for C4S are shown in Supplementary Figure 1.

Both beverages were manufactured at a US FDA cGMP-compliant facility. The finished C4S and PLA products were independently verified by third-party testing at DYAD Labs (Merieux NutriSciences Company, Salt Lake City, UT, USA) for caffeine, niacinamide, and cyanocobalamin (e.g., Vitamin B_{12}) content, nutrition facts, physical properties and organoleptic, and specification identity, composition, potency, and purity using validated analytical methods. These analyses confirmed that C4S met all analytical specifications for total Calories, macronutrient quantities, and active ingredients; PLA likewise met all analytical specifications for total Calories and macronutrient quantities, and contained negligible or trace amounts of caffeine, niacin, and vitamin B12. In addition, organoleptic and physical property testing verified that C4S and PLA provided similar sensory experiences. Absence of World Anti-Doping Agency (WADA) banned substances was independently confirmed by LGC Science, Inc. (Informed Sport; Lexington, KY, USA) using validated methods. Analytical results were reviewed by CML prior to the beverages being approved for use within the present study. The manufacturer, grant donor, and CML formulated and maintained blinding of groups. Each beverage was randomly assigned an item letter, A or B, by the manufacturer. To blind investigators, both C4S and PLA were packaged in identical 16 oz cans and participants were randomized to each condition by letter. Blinding was maintained until data collection and statistical analysis was completed. CML was not involved in data collection or statistical analysis.

Cognitive performance

Cognitive performance was assessed using CNS Vital Signs (CNSVS, v. 4.0.95, Morrisville, NC, USA), a validated, reliable computerized neurocognitive test battery for use in clinical and research settings. The battery was adapted from 10 normed neurocognitive tests (41–43) and produced assessment scores across 15 clinical domains of neurocognitive function. The tests included were: Verbal Memory Test (VBM), Visual Memory Test (VSM), Finger Tapping Test (FTT), Symbol Digit Coding (SDC), Stroop Test (ST), Shifting Attention Test (SAT), Continuous Performance Test (CPT), Perception of Emotions Test (POET), Non-Verbal

Reasoning Test (NVRT), and Four Parts Continuous Performance Test (FPCPT).

The domains measured included: composite memory, verbal memory, visual memory, psychomotor speed, reaction time, complex attention, cognitive flexibility, processing speed, executive function, simple attention, motor speed, social acuity, reasoning, sustained attention, and working memory. For all domains except for complex attention and reaction time, higher scores indicate greater cognitive performance. For complex attention and reaction time, lower scores represented greater cognitive performance. The calculations used to determine performance in each cognitive domain are shown in Supplementary Table 1.

Video gaming performance

Participants played five different video games of varying genres and complexities, which included Tetris, Four-in-a-Row, Rayman Legend, FIFA-14, and Call of Duty: Advanced Warfare. The primary video game outcome was Tetris score, owing to its widespread familiarity, relative simplicity, and its use in neurocognitive research (44–46). Importantly, Tetris is a popular game with simple objectives and operational rules (47) making it less subject to learning effects. Further, Tetris gameplay is cognitively demanding (44, 48) and is thought to stress visuospatial working memory (46, 49, 50), which is a limited-capacity cognitive system also associated with more complex action video games (51–53). The other games used were considered exploratory, as less is known regarding the cognitive demands of these games, and performance metrics in them have not been previously used as dependent variables in the context of intervention studies. However, selection of these games was based on their use in a previous cross-sectional study (54). Both Tetris and Four-in-a-Row were played on tablets (iPad 8th Generation Model MYLD2LL/A, Apple, Cupertino, CA, USA), whereas Rayman Legends, FIFA-14, and Call of Duty Advanced Warfare were played on a PC (Dell Technologies, Intel®Core (TM) i7-10700 CPU; 64-bit OS) with a gaming monitor (Alienware AW2720-HF, Dell Technologies, Round Rock, TX, USA) and noise-cancelling gaming headphones (Momentum Wireless, Sennheiser electronic, Wedemark, Germany).

Tetris

Tetris (Electronic Arts, Redwood City, CA, USA) is a two-dimensional visuospatial puzzle game. Participants were given four minutes of play time on Marathon mode and instructed to maximize the score (points) displayed on the screen. The total score at the end of play time was recorded.

Four-in-a-Row

Four-in-a-Row (Optime Software, LLC, Great Falls, VA, USA) is a two-dimensional problem-solving game. Participants were given two minute of play time on easy level and two minutes of play time on medium level and instructed to maximize the number of rounds won (wins) on each level. The number of wins and losses for each difficulty level was recorded.

Rayman Legends

Rayman Legends (Ubisoft, Montreuil, France) is a two-dimensional platform game. Participants were given four minutes of play time and instructed to maximize the score (points) displayed on the screen. The total score at the end of play time was recorded.

FIFA-14

FIFA-14 (Electronic Arts, Redwood City, CA, USA) is a 3-dimensional sports game. Participants played two rounds of Penalty Shootout Mode on Bronze level followed by two rounds of Dribbling mode on Bronze level with the goal of maximizing the score (points) displayed on the screen during each round. To maintain consistency of playing conditions, the same player avatar was selected at each visit. The total score for each round was recorded and the maximum score was used to compare performance between conditions.

Call of Duty Advanced Warfare

Call of Duty Advanced Warfare (Activision, Santa Monica, CA, USA) is a 3-dimensional first-person shooter game. Participants played one round in Exo Survival Mode on moderate difficulty. To maintain consistency of playing conditions, the same map (Detroit) was used at each visit, and participants were instructed to avoid all upgrade packages. Participants were instructed to maximize play time and number of strikes ("kills"). The round ended upon the second defeat (death) of the player's avatar. Total strikes and total score were recorded.

Profile of mood states

Moods were assessed using the Profile of Mood States (POMS 2nd Edition, Multi-Health Systems, North Tonawanda, NY, USA), a commonly used and validated (55–57) psychological screening instrument to examine transient affective states comprised of 35 items (adjectives). At the end of each experimental visit, participants indicated the extent to which they felt each item during the elapsed time since consuming the beverage on a 5-point scale ranging from "not at all" (scored 0) to "extremely" (scored 4). Seven mood states were assessed: Anger-Hostility, Confusion-Bewilderment, Depression-Dejection, Fatigue-Inertia, Tension-Anxiety, Vigor-Activity, and Friendliness. Total Mood Disturbance, an indication of global psychological distress, was derived as the sum of Anger-Hostility, Confusion-Bewilderment, Depression-Dejection, Fatigue-Inertia, Tension-Anxiety, and Vigor-Activity, with Vigor-Activity weighted negatively (57). Mood State and Total Mood Disturbance scores from post-drink consumption surveys were compared between C4S and PLA visits.

Cardiovascular safety assessments

Cardiovascular outcomes included blood pressure, oxygen saturation, heart rate, and cardiac electrical activity *via* electrocardiogram (ECG). Blood pressure, oxygen saturation, and heart rate measures were recorded at baseline, 40 min after beverage consumption, immediately following completion of the cognitive tests, immediately following completion of the last video game (Call of Duty: Advanced Warfare), and at the end of the visit (following 10 min of rest after video games). ECGs were obtained at baseline, 40 min after consuming the beverage, and immediately after completing the last video game (Call of Duty: Advanced Warfare).

Blood pressure

Blood Pressure (BP) was measured using an automatic, upper-arm, electronic sphygmomanometer (Omron Platinum BP5450, Omron Healthcare, Lake Forest, IL, USA) placed on the left arm with participants relaxed in an upright seated position and their feet flat on the floor. Two BP readings were taken at each BP assessment. If the variance in either systolic or diastolic blood pressure (SBP or DBP) between the two readings exceeded 5 mmHg, a third reading was obtained. Average BP (mmHg) for each assessment was determined by calculating the mean of the two BP readings. For instances where three BP readings were recorded, the two readings with the lowest variance in SBP between them were used to find the mean.

Oxygen saturation, heart rate, and rate pressure product

Oxygen saturation (SpO_2) and heart rate (HR) were measured using a fingertip pulse-oximeter (Innovo iP900AP, Innovo Medical, Stafford, TX, USA). Measurements were taken on the right index finger with participants in an upright seated position. Two SpO_2 readings and HR readings were taken during each assessment. Average SpO_2 (%) for each assessment was determined by calculating the mean of the two readings. Average HR (BPM) for each assessment was likewise determined by calculating the mean of the two readings. The rate pressure product (RPP) was determined as the product of the HR and SBP.

Cardiac electrical activity

Cardiac electrical activity was assessed with a 12-lead Electrocardiogram (ECG) (CardioTech SE-12 Series, Edan Instruments, Pingshan District, P.R. China). A 30-second continuous ECG was obtained with participants in an upright seated position. The primary outcome obtained from each ECG recording was heart-rate corrected QT interval (QTc, ms). QTc is an indirect measure of ventricular repolarization which is associated with incidence of cardiac arrythmias and sudden death. Secondary outcomes from ECG recordings were PR interval (ms), QRS interval (ms), and QRS-axis (degrees).

Blinding efficacy and adverse events

Upon completion of the last experimental visit, participants were unblinded and completed a condition blinding questionnaire indicating which drink they believed they consumed at each visit. At the end of each experimental visit, participants completed an Adverse Events (AE) survey including a list of nine common AEs and an "Other" field. Participants indicated whether they had experienced each AE during the visit with a "Yes"/"No" response. For any "Yes" response participants indicated the likelihood ("Possible", "Likely", or "Very Likely") that the AE may have been caused by the test beverage. AE responses were scored on a 0-3 scale, with "No" scored as 0, and "Yes; Possible", "Yes; Likely", and "Yes; Very Likely" scored as 1, 2, and 3, respectively. Results are displayed in Table 5.

Statistical analyses

All variables were assessed for normality using the Shapiro-Wilk test. Paired-samples t-tests were used to examine between-condition differences in cognitive function and gaming performance for normally distributed variables. For non-normally distributed variables, Wilcoxon signed ranked tests were used instead and p_W is used to denote the use of Wilcoxon tests in the results section. Single-tailed Spearman correlations were used to examine the associations among the between-condition changes in select cognitive domain parameters and Tetris gaming-performance due to our hypothesis of direct associations between them. Significant change scores for cognitive performance and video game performance outcomes are reported as the average absolute individual change (±95% CI), the average relative individual change, and the relative mean difference (e.g., C4S – PLA/PLA * 100) in the following format: (avg individual change ± 95% CI [avg relative individual change; relative mean difference]; *p*value). Significant change scores for mood state outcomes are reported as the average absolute individual change (±95% CI) and the relative mean difference in the following format: (avg individual change ± 95% CI [relative mean difference]; *p*value). Cardiovascular outcomes were statistically analyzed using 2 (condition) × 5 (time) repeated measures analyses of variance (RM ANOVAs) for BP, HR, RPP, and SpO_2, or 2 (condition) × 3 (time) RM ANOVAs for ECG variables. When appropriate, follow-up analyses included lower order repeated measures ANOVAs and/or Tukey-corrected dependent samples t-tests. All statistical analyses were performed using JASP and GraphPad Prism (v.9.2.0, San Diego, CA, USA) and the a priori alpha was set at 0.05. Due to the number of cognitive domains (e.g., 15 domains) assessed without pre-specification of a primary cognitive outcome of interest, we report unadjusted *p*value and also interpret relative to a Sidak-corrected alpha ($\alpha = 0.0034$) to control the family-wise error rate for cognitive domain outcomes. Similarly, we report unadjusted *p*value for mood states assessed by the POMS (8 outcomes) and also interpret relative to a Sidak-corrected alpha ($\alpha = 0.0064$) to control the family-wise error rate for mood

states. A priori sample size analysis was performed to determine that a total sample size of approximately 45 participants would be needed to observe an effect size (d_z) of 0.5 between treatments with power = 0.90 and $\alpha = 0.05$.

Results

Lifestyle controls

There were no significant between-condition differences in nutritional intake measures, which included kcals ($p = 0.80$), protein (p_W = 0.81), carbohydrates ($p = 0.47$), and fat (p_W = 0.44), during the week preceding each experimental visit. There were likewise no between-condition differences in caffeine intake (p_W = 0.50) during the week preceding each experimental visit. Average values of energy (kcals/day), protein (g/day), carbohydrates (g/day), fat (g/day) and caffeine (mg/day) based on participant food log entries are displayed in Table 2. There were no significant between-condition differences in physical activity (p_W = 0.29), sleep duration ($p = 0.49$), sleep disruptions (p_W = 0.71), or quality of sleep ($p = 0.21$). Reported values from physical activity and sleep logs are displayed in Table 3.

Cognitive performance outcomes

Acute C4S consumption improved cognitive flexibility (+4.3 ± 2.1 arbitrary units (a.u.) [+9.6%; +8.2%]; $p < 0.001$), executive function (+4.3 ± 2.0 a.u. [+9.1%; +7.9%]; $p < 0.001$), sustained attention (+2.1 ± 1.5 a.u. [+9.8%; +6.8%]; p_W = 0.01), motor speed (+2.9 ± 2.0 taps [+2.7%; +2.4%]; p_W < 0.001), psychomotor speed (+3.9 ± 3.8 a.u. [+2.3%; +2.0%]; $p = 0.04$), and working memory (+1.0 ± 0.9 a.u. [+16.0%; +8.3%]; p_W = 0.02) (Figure 3). C4S consumption also tended to improve complex attention (-1.2 ± 1.3 errors [-2.2%; −14.2%]), although this effect was not significant. Cognitive flexibility, executive function, and motor speed remained significant at the Sidak-corrected α of 0.0034. There were no significant effects on complex attention (p_W = 0.07), nor on composite memory, visual memory, verbal memory, reaction time, reasoning, processing speed, social acuity, or simple attention (all $p \geq 0.12$).

Video game performance outcomes

Acute C4S consumption improved Tetris scores (+1,081 ± 1,128 points [+48.3%; +19.3%]; p_W = 0.049), and the C4S-induced improvement was associated with the improvements in psychomotor speed ($\rho = 0.29$; $p = 0.03$) (Figure 4). There were no significant effects of C4S consumption on Four-in-a-Row, Rayman Legends, FIFA, or Call of Duty scores (all $p \geq 0.20$, Table 4).

Mood state outcomes

Acute C4S consumption improved Total Mood Disturbance (-3.7 ± 2.5 a.u. [-344.8%]; p_W = 0.002). Three individual mood states were also improved following C4S consumption (Figure 5), which included Fatigue-Inertia (-1.4 ± 1.0 a.u. [-36.4%]; p_W = 0.004), Vigor-Activity (+2.4 ± 1.2 a.u. [+32.9%]; $p < 0.001$), and Friendliness (+0.7 ± 0.7 a.u. [+6.8%]; p_W = 0.04). Total Mood Disturbance, Fatigue-Inertia, and Vigor-Activity remained significant at the Sidak-adjusted α of 0.0064. C4S had no significant effects on Anger-Hostility, Tension-Anxiety, Confusion-Bewilderment, or Depression-Dejection compared to PLA (all $p \geq 0.27$).

Cardiovascular safety outcomes

There was a significant condition × time interaction for HR ($F_{4,168}$ = 2.542, $p = 0.042$). HR did not change relative to baseline in the PLA condition but decreased 5.2 bpm from baseline to post-drink consumption in C4S and remained 2.2 – 5.0 bpm lower than baseline throughout the experimental visit (Figure 6a). Consequently, there were no differences in HR between C4S and PLA except at baseline, where HR was 3.2 bpm greater in C4S than PLA ($p = 0.02$).

There was a significant condition × time interaction for SBP ($F_{4,168}$ = 6.458, $p < 0.001$). SBP did not change relative to baseline in the PLA condition but increased 3.7 mmHg following C4S consumption and remained elevated throughout the experimental visit (Figure 6b). Consequently, SBP was 3.7, 4.8, 5.4, and 4.6 mmHg greater in C4S than PLA

Table 2. Dietary intake data prior to C4S versus PLA conditions. Values are mean ± SD.

	C4S	PLA	p-value
Absolute Energy (kcals/day)	2,101 ± 603	2,082 ± 566	0.80
Relative Energy (kcals/kg/day)	28.1 ± 8.7	28.1 ± 9.1	0.96
Absolute Protein* (g/day)	102 ± 45	103 ± 46	0.81
Relative Protein* (g/kg/day)	1.4 ± 0.6	1.4 ± 0.6	0.62
Absolute Carbohydrates (g/day)	240 ± 77	232 ± 74	0.47
Relative Carbohydrates (g/kg/day)	3.2 ± 1.1	3.1 ± 1.1	0.51
Absolute Fat* (g/day)	82 ± 35	83 ± 27	0.44
Relative Fat* (g/kg/day)	1.1 ± 0.5	1.1 ± 0.5	0.46
Absolute Caffeine* (mg/day)	66 ± 66	57 ± 69	0.50
Relative Caffeine* (mg/kg/day)	0.9 ± 0.9	0.7 ± 0.9	0.42

*indicates Wilcoxon signed rank test used for non-normally distributed variables.

Table 3. Outcomes from participant physical activity and sleep logs. Values reported are mean ± SD.

Lifestyle Factor	C4S	PLA	p-value
Physical Activity* (MET·min / week)	1,347 ± 1056	1,256 ± 960.5	0.29
Sleep Duration (hrs / night)	7.5 ± 0.8	7.5 ± 0.8	0.49
Sleep Disruptions* (times woke / night)	0.5 ± 0.5	0.5 ± 0.5	0.71
Sleep Quality (quality / night)	3.8 ± 0.7	3.9 ± 0.7	0.21

Sleep Quality was rated on a scale from 1 (poorest) to 5 (greatest). *indicates Wilcoxon signed rank test used for non-normally distributed variables.

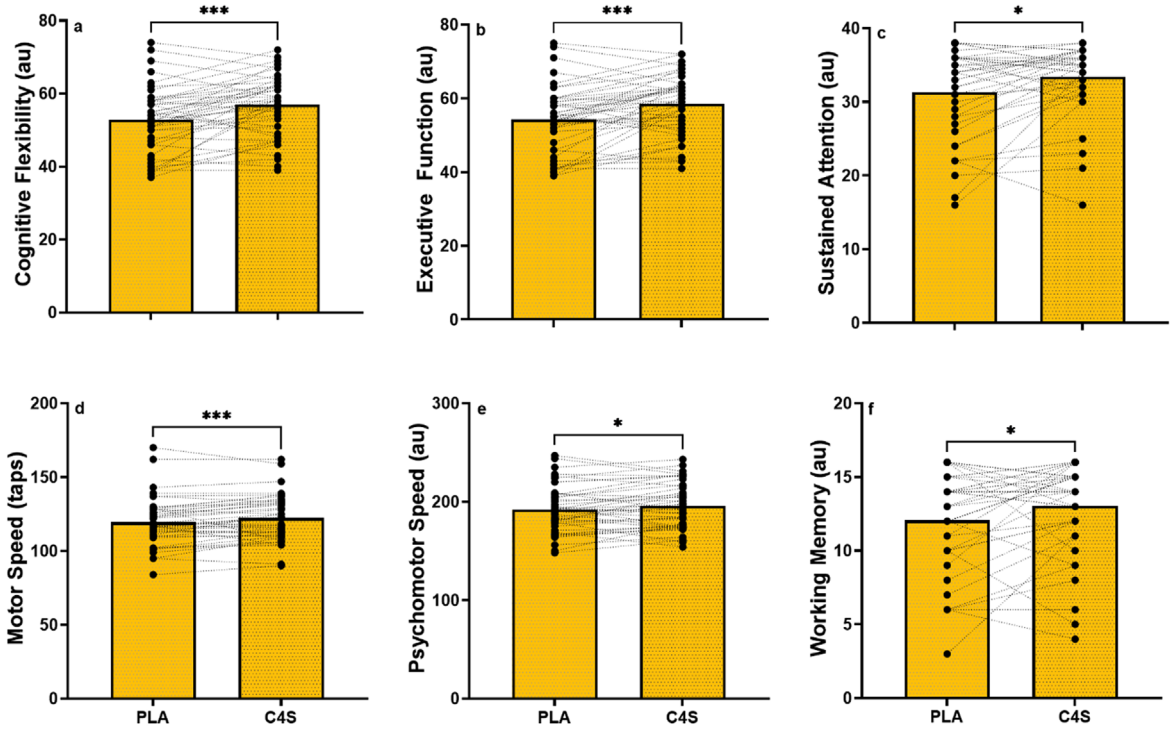

Figure 3. Differences between PLA and C4S for the six neurocognitive domains that were improved following acute C4S consumption. Graphs (a–f) depict cognitive flexibility, executive function, sustained attention, motor speed, psychomotor speed and working memory, respectively. *$p < 0.05$; ***$p < 0.001$.

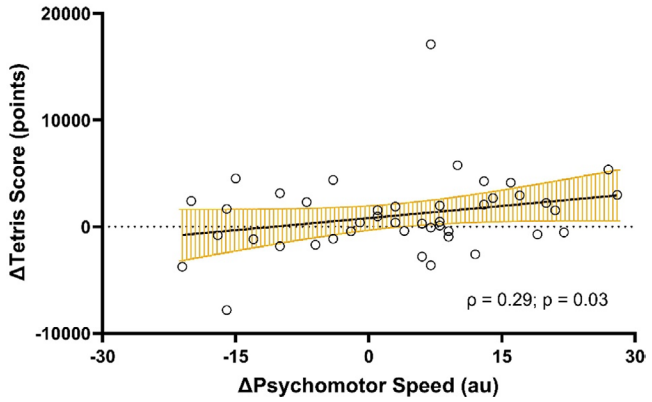

Figure 4. The association between changes (e.g., C4S – PLA) in Tetris scores and changes in psychomotor speed. The error bars depict 95% confidence intervals.

at post-drink, post-cognitive tests, post-video games, and the final observation period, respectively.

There was also a significant condition × time interaction for DBP ($F_{4,168}$ = 3.536, $p = 0.009$). Similar to SBP, DBP did not change relative to baseline in the PLA condition but increased 3.7 mmHg following C4S consumption and then remained elevated throughout the experimental visit (Figure 6c). Consequently, DBP was 5.0, 3.7, 4.5, and 2.9 mmHg greater in C4S than PLA at post-drink, post-cognitive tests, post-video games, and the final observation period, respectively.

There was no condition × time interaction for RPP ($F_{4,168}$ = 1.44, $p = 0.22$), but there were main effects for time ($F_{4,176}$ = 12.71, $p < 0.001$) and condition ($F_{1,44}$ = 15.21, $p < 0.001$). Independent of the condition, RPP decreased from baseline to post-drink consumption (-304.3 bpm·mmHg, $p = 0.004$), remained depressed following cognitive testing, and then increased (+480.8 bpm·mmHg, $p < 0.001$) back to baseline values following completion of the video games where it remained in the final observation period. The condition main effect indicated that RPP was greater in C4S than PLA (8,267 vs. 7,862 bpm·mmHg) independent of time (Figure 6d).

There was no condition × time interaction for SpO_2 ($F_{4,168}$ = 1.42, $p = 0.23$), but there was a main effect for time ($F_{4,176}$ = 10.44, $p < 0.001$). SpO_2 increased from baseline to

Table 4. Gaming performance outcomes. Values are mean ± SD.

Gaming Performance Metric	C4S	PLA	Difference	p-value
Tetris Score*	6681 ± 4422	5601 ± 4522	1081 ± 3666	***0.049***
4IR Easy Wins*	1.95 ± 1.88	1.67 ± 1.54	0.28 ± 1.91	0.48
4IR Middle Wins*	0.70 ± 0.89	0.51 ± 0.70	0.19 ± 0.88	0.23
Rayman Score*	318.5 ± 97.2	305.0 ± 108.5	13.5 ± 81.4	0.36
FIFA Penalty	11430 ± 1864	11126 ± 1950	303 ± 1802	0.28
FIFA Dribbling	7155 ± 2256	6510 ± 2888	645 ± 3195	0.20
COD Score*	13937 ± 14467	11554 ± 10674	2384 ± 13610	0.45
COD Strikes*	40.45 ± 34.42	35.95 ± 26.62	4.5 ± 32.1	0.50

4IR, Four-in-a-Row; COD, Call of Duty. *indicates Wilcoxon signed rank test used for non-normally distributed variables.

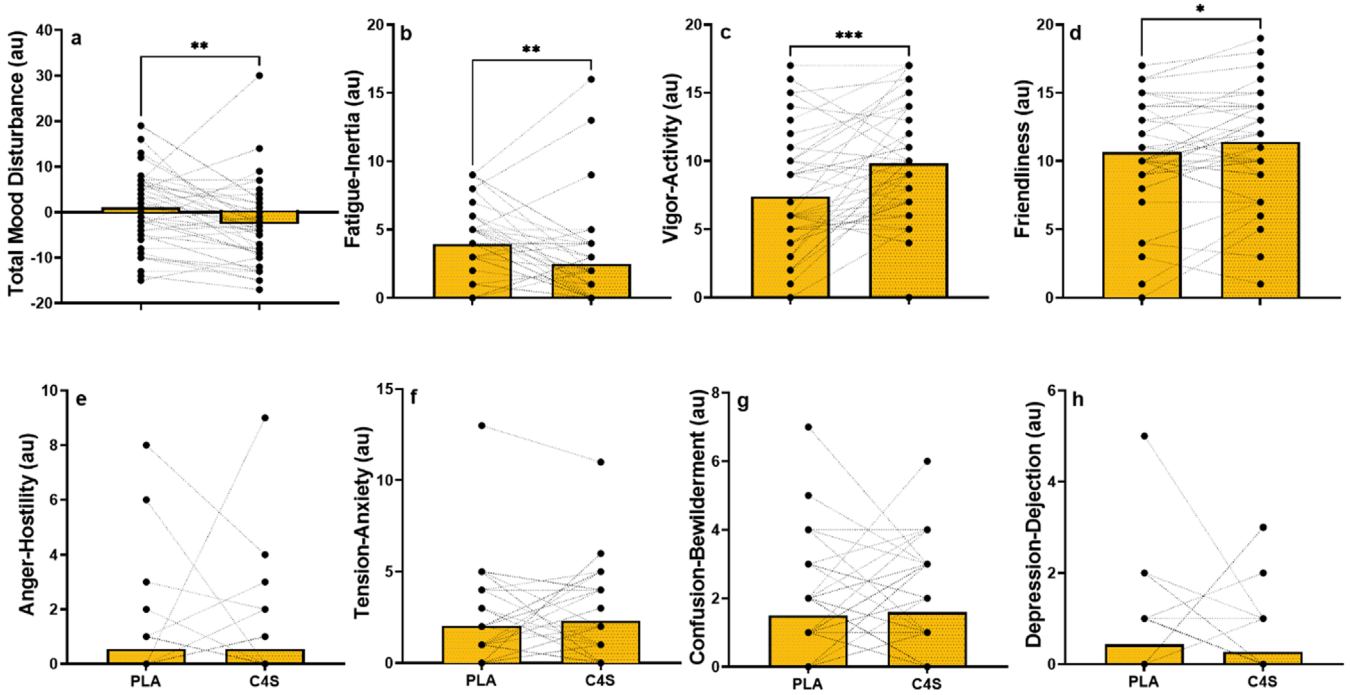

Figure 5. The (a) Total Mood Disturbance, (b) Fatigue-Inertia, (c) Vigor-Activity, (d) Friendliness, (e) Anger-Hostility, (f) Tension-Anxiety, (g) Confusion-Bewilderment, and (h) Depression-Dejection scores following placebo (PLA) versus novel energy drink (C4S) consumption. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

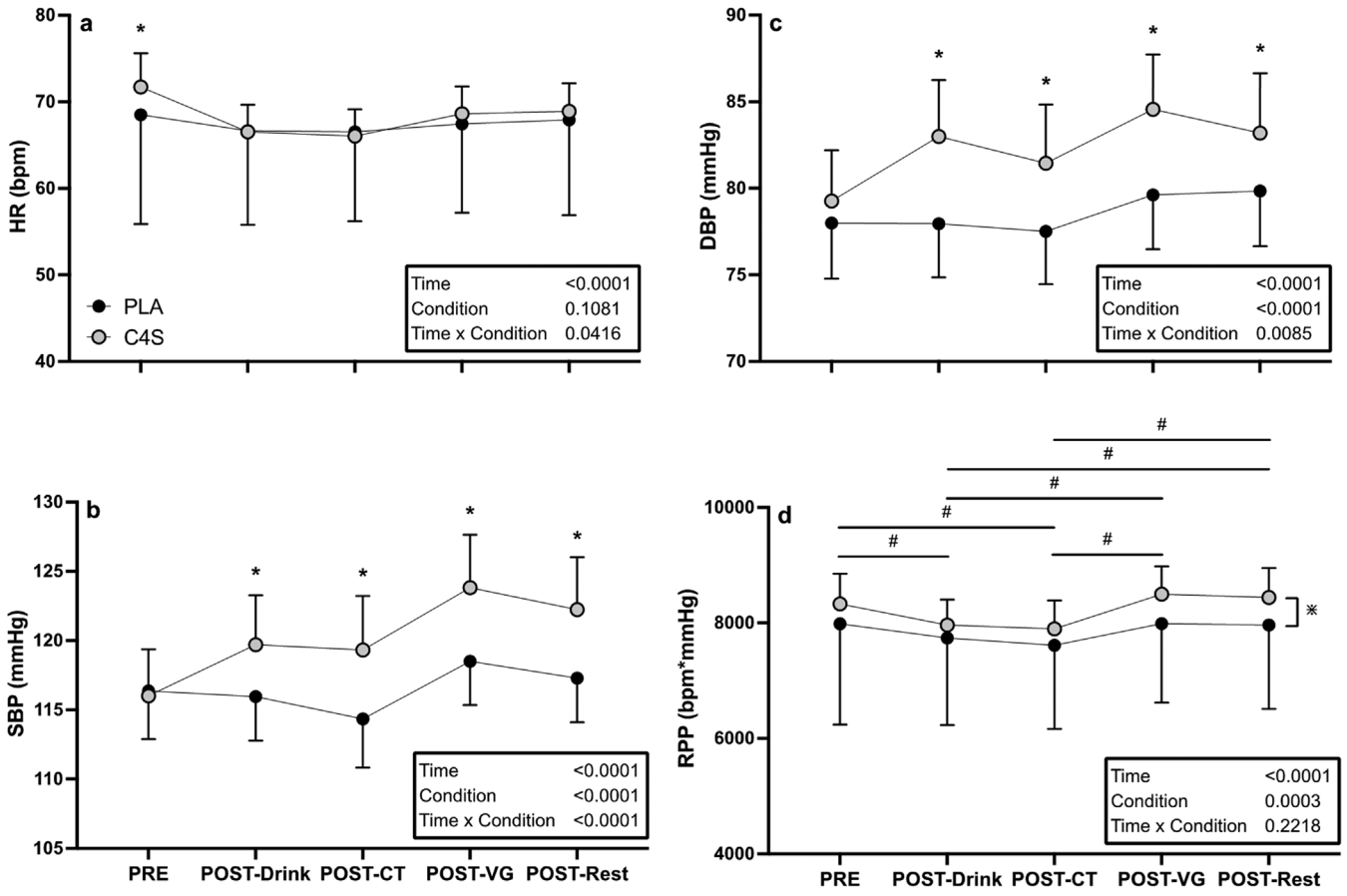

Figure 6. Graphs (a–d) show heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and rate-pressure-product (RPP), respectively, during PLA and C4S visits. Each were measured pre-drink consumption (PRE), 40 min post-drink consumption (POST-Drink), post-cognitive testing (POST-CT), post-video game completion (POST-VG) and following a final 10-minute rest period (POST-Rest). *denotes $p < 0.05$ for time × condition interactions; #denotes $p < 0.05$ main effect for time.

post-drink consumption (+0.4%, $p = 0.002$) and remained elevated throughout the study relative to baseline (+0.3 – 0.7%, $p = <0.001 – 0.06$) independent of condition.

There were no condition × time interactions for QTc ($F_{2, 85} = 0.53$, $p = 0.59$), QRS interval ($F_{2, 85} = 0.15$, $p = 0.86$), PR interval ($F_{2, 85} = 0.51$, $p = 0.60$), or QRS Axis ($F_{2, 85} = 0.45$, $p = 0.64$). However, there was a main effect for time for QRS interval ($F_{2, 88} = 7.14$, $p = 0.001$), which increased (+1.3 ms, $p = 0.03$) from baseline to post-drink consumption and remained elevated following completion of the video games independent of condition (Figure 7b).

Blinding efficacy and adverse events

76% of participants correctly guessed when they received C4S and PLA on condition blinding surveys. Since third-party analytical testing confirmed that PLA and C4S were organoleptically, volumetrically, and calorically matched using validated methods, these results suggest that the observed effects on cognitive function and mood were acutely noticeable by participants. Table 5 shows the number and percentage of participants who reported experiencing each Adverse Event (AE), along with the average likelihood that the AE was

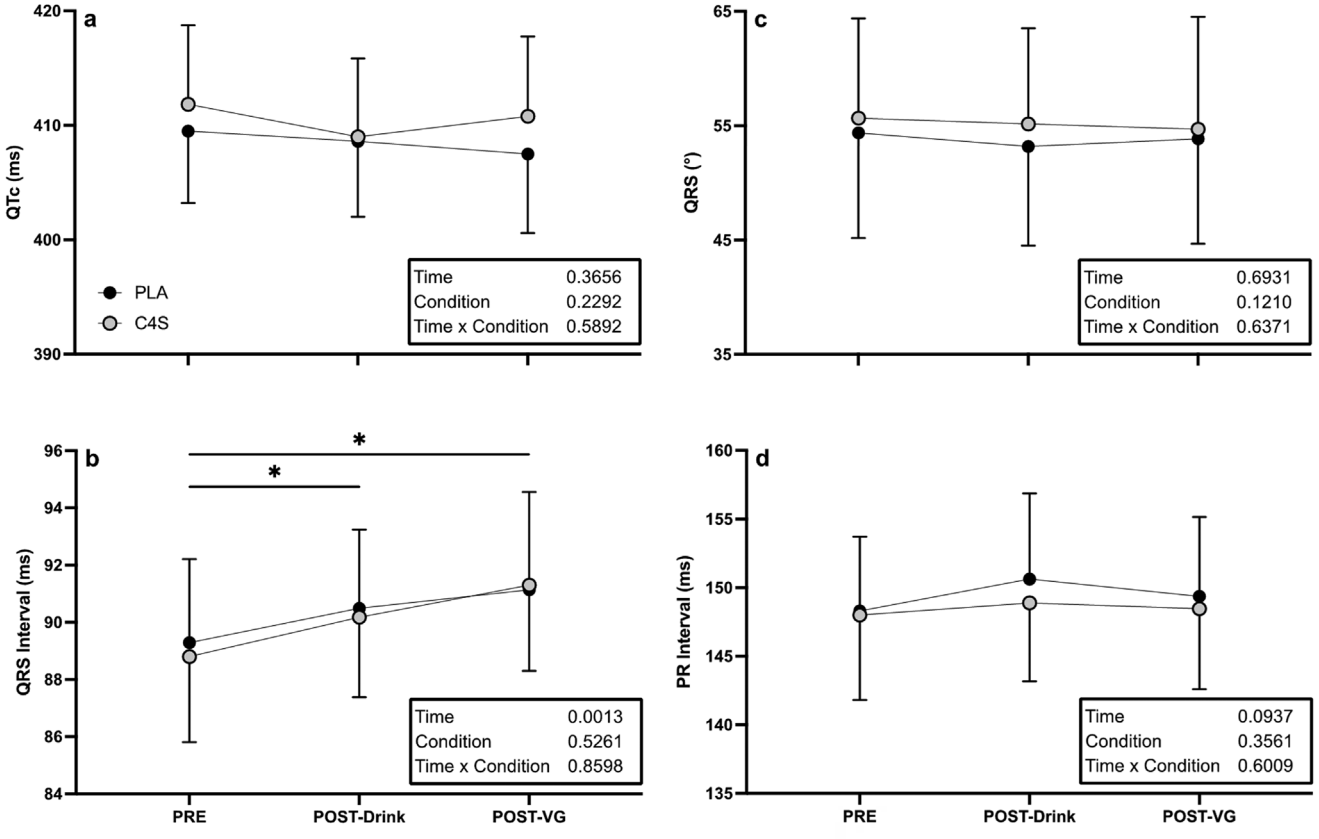

Figure 7. Graphs (a–d) show corrected QT interval (QTc), QRS Interval, QRS Axis, and PR Interval, respectively, during PLA and C4S visits. Each were measured pre-drink consumption (PRE), 40 min post-drink consumption (POST-Drink), and post-video game (POST-VG) completion.
*denotes $p < 0.05$ main effect for time.

Table 5. Frequency and likelihood of AEs following test beverage consumption.

	C4S		PLA	
Adverse Event	Frequency n (%)	Average Likelihood	Frequency n (%)	Average Likelihood
Nausea	3 (6.8%)	2.3	1 (2.3%)	3.0
Vomiting	1 (2.3%)	2.0	0	–
Headache	4 (9.1%)	1.3	9 (20.5%)	1.1
Stomachache / Gas / Bloating	12 (27.3%)	2.0	8 (18.2%)	1.8
Diarrhea	0	–	0	–
Constipation	0	–	0	–
Itching	3 (6.8%)	1.3	0	–
Fatigue	4 (9.1%)	1.0	12 (27.3%)	1.3
Heart Palpitation	2 (4.5%)	2.0	1 (2.3%)	2.0
Other	2 (4.5%)	2.0	1 (2.3%)	1.0

Frequency refers to number of participants who reported particular adverse event in each condition. Average likelihood refers to the participants' perceived likelihood that the AE was due to C4S or PLA consumption on a 0 – 3 scale, where 0 indicates no likelihood and 3 indicates very likely.

caused by the test beverage. The "Other" AEs reported for C4S were "jittery" and "cramping" and for PLA, "heavy eyes".

Discussion

The purpose of this study was to examine the efficacy of acute C4S consumption for improving cognitive and gaming performance and mood. Another unique and novel aspect of this study was the determination of C4S' effects on cardiovascular safety outcomes both at rest and following acute mental stress (e.g., cognitive and video game testing). The primary findings of the present study indicated that relative to placebo, C4S consumption improved six neurocognitive domains, including cognitive flexibility by 8.2%, executive function by 7.9%, sustained attention by 6.8%, motor speed by 2.4%, psychomotor speed by 2.0%, and working memory by 8.3%, with improvements in three of these (cognitive flexibility, executive function, and motor speed) remaining significant following adjustment to control the family-wise error rate. C4S consumption was also associated with a 19.3% improvement in performance during a cognitively demanding, two-dimensional visuospatial video game (Tetris). Moreover, the improvements in Tetris were significantly related to improvements in psychomotor speed ($\rho = 0.29$). Acute C4S consumption was also associated with significant improvements in mood, which included a 36.4% improvement in Fatigue-Inertia, a 32.9% improvement in Vigor-Activity, a 6.8% improvement in Friendliness, and a 344.8% improvement in Total Mood Disturbance relative to placebo. Improvements in fatigue-inertia, vigor-activity, and Total Mood Disturbance all remained significant following adjustment to control the family-wise error rate. Heart rate (HR) was greater at baseline in C4S than placebo and decreased from baseline to post-drink consumption in C4S only. Consequently, there were no observed differences in HR between C4S and placebo following drink consumption. However, C4S did increase systolic blood pressure (SBP) and diastolic blood pressure (DBP). Therefore, rate-pressure-product (RPP) was greater in C4S versus placebo independent of time, but there was no increase in RPP relative to baseline following drink consumption in either condition. Finally, there was no effect of C4S on the corrected QT interval (QTc). Thus, overall, our results suggest that acute C4S consumption was efficacious for neurocognitive performance, visuospatial gaming (Tetris) performance, and mood enhancement, and had no adverse effects on HR or QTc despite being associated with 3.7- 5.4 mmHg and 2.9 – 5.0 mmHg increases in SBP and DBP, respectively.

In accordance with our hypothesis, acute C4S consumption resulted in improved cognitive performance across several domains that reflected enhancements in adaptability, rapid decision making, directed focus, motor speed, visual-perceptual response time, and working memory. A slight improvement was also observed in complex attention, although the effect was not large enough to be considered significant ($p = 0.07$). No significant effects were observed for composite memory, verbal memory, visual memory, reaction time, processing speed, simple attention, social acuity, or reasoning. Despite interest in understanding the "interactive effects" of combined energy drink ingredients (58) and the fact that energy drinks are exclusively consumed in finished product form, very few studies have examined the cognitive effects of finished energy drink products. Red Bull is the most extensively studied finished product to date, but the cognitive effects have not been consistent (59). Wesnes et al. (59) reported that acute consumption of Red Bull containing 27 g glucose resulted in significant improvements in memory performance over both caffeine-matched sugar-free Red Bull and a placebo, indicating that glucose may have been responsible for the cognitive improvements. Scholey and Kennedy (16) demonstrated that a caffeine and glucose containing energy drink augmented secondary memory and speed of attention without any other cognitive benefits. Conversely, in an elegantly designed study examining the differential contributions of glucose, caffeine, and taurine on cognitive function, Giles et al. (60) concluded that caffeine is the likely driver of the cognitive effects of energy drinks. Subsequently, in a study using the same cognitive testing platform as in the present study, Konishi et al. (61) reported that an acute, 200 mg dose of caffeine had limited cognitive effects in young, healthy volunteers, causing a significant improvement only in the Shifting Attention Test. Finally, in one of a limited number of studies to have examined the effects of a finished energy drink product on cognitive performance in gamers, Thomas et al. (62) reported that an energy drink containing a proprietary blend that included L-carnitine, 150 mg caffeine, L-theanine, choline, phosphatidylserine, and other ingredients had no effect on either working memory or reaction time. Strikingly, the novel energy drink used in our study resulted in substantial cognitive effects across a wider range of cognitive domains than 200 mg of caffeine alone (61) and potentially than a sugar-containing, caffeinated soft drink (16) despite containing no sugar and minimal (i.e., <10) calories. These findings support that this novel combination of ingredients, which include 200 mg of caffeine, Citicoline/CDP-Choline, niacinamide, and cyanocobalamin, produce robust cognitive improvements beyond those of caffeine alone, and without the potential harms of excess sugar consumption. The results of the present study also highlight the need for further examination of finished-product energy drinks, as the combination of ingredients purported to enhance cognitive function may be more efficacious than the sum of their parts.

Although the marketing of energy drinks to gamers is well documented (17, 63), few studies have examined the effect of energy drink consumption or nutritional supplementation on cognitive performance in gamers (62, 64, 65). Similarly, only one other study to our knowledge has examined the effects of a caffeine-based dietary supplement on gaming performance in video gamers (66). Further, there are a paucity of studies that have examined the direct effects of acute ready-to-drink finished-product energy drink consumption on video gaming performance. We hypothesized that acute consumption of C4S would result in improved gaming performance. Tetris score was considered the primary video game performance outcome in this study due to its popularity, relative simplicity, and its establishment in

the neuroscience literature as a stressor of visuospatial working memory (46, 49, 50), a limited-capacity cognitive system. In fact, Tetris has been suggested as an approach to study cognitive control, strategy, time-sensitive decision making, and the interactions between perception, cognition, and action (48). Our data show that acute consumption of C4S resulted in a 48% average individual improvement in Tetris scores over placebo. Perhaps unsurprisingly, we also observed an association between the improvement in Tetris score and improvements in psychomotor speed ($\rho = 0.29$; $p = 0.03$), which is a measure of timely response to visual-perceptual information. Each of the other games used in this study, which included Four-in-a-Row, Rayman Legends, FIFA, and Call of Duty, were considered exploratory because we were unsure of how they may stress cognition, nor of their sensitivity due to the relative unfamiliarity with these games among participants. Acute consumption of C4S did not result in significantly improved performance in these games, but given the limitations related to their use, it is difficult to interpret these findings. Future studies may wish to consider examining the efficacy of energy drinks on video gaming performance in gamers who are highly familiar with a particular game (e.g., as in professional gamers) to maximize sensitivity and ecological validity. To do so, reliability and validity studies will also be necessary to identify sensitive video gaming (i.e., e-sports) performance metrics and to understand the degree to which they reflect neurocognitive performance domains. Still, our findings are notable both given the lack of randomized controlled trials that have examined the effects of supposed nootropic supplements on video gaming performance (67), and also in light of a recent study indicating that neither caffeine nor a caffeinated dietary supplement high in chlorogenic acids elicited any improvements in gaming performance (66). Overall, our results suggest that C4S is effective for enhancing performance in the cognitively demanding video game Tetris, an effect that may have been supported by improvements in psychomotor speed.

Our data also show that acute C4S consumption improved several measures of mood reflecting elevated energy, friendliness, and subjective wellbeing, and reduced fatigue. The observed improvements in scores of vigor and fatigue are congruent with several prior studies that have reported improved vigor, energy, or subjective alertness following consumption of energy drinks containing caffeine (68–71). However, to our knowledge, ours is the first to demonstrate a significant improvement in friendliness. Our data also indicate that acute C4S consumption had no effects on anger-hostility, tension-anxiety, confusion-bewilderment, or depression-dejection, suggesting that C4S did not influence negative mood states. Our findings regarding acute mood enhancement are in contrast to a strong body of literature which suggests that *chronic* energy drink consumption has adverse mood effects. For example, a dose-response relationship between chronic caffeinated energy drink consumption and sleep disturbance and anxiety has been reported in young adults (72). A systematic review and meta-analysis of randomized control trials (7 studies) revealed that energy drink consumption significantly increased incidence of insomnia and jitteriness, but did not show statistically significant effects on anxiety or nervousness (73). Given that a significant portion of adolescents play video games (74) and increasingly consume energy drinks (75), and with early evidence suggesting that chronic energy drink consumption may be associated with adverse mood effects in this population (76), future studies will be needed to identify the acute and chronic mood-related effects of energy drink consumption in adolescents. Future studies are also needed to understand how the consumption of these drinks influence sleep, which is an important lifestyle factor that promotes both mental and cardiometabolic health. Regardless, in this study, acute C4S consumption had robust effects on positive mood states without influencing negative mood states in adult gamers.

We hypothesized that C4S would increase BP, HR, and thus myocardial oxygen demand. In accordance with our hypothesis, acute C4S consumption increased in SBP and DBP by 3.7-5.4% and 2.9-5.0%, respectively. The observed increases in BP are partially congruent with a meta-analysis conducted by Shah et al. (77). The authors note a dose-response relationship of energy drink consumption on SBP, where SBP increases most dramatically for drinks containing 200 mg or more caffeine. Therefore, although C4S contained 200 mg of caffeine and increased blood pressure, the 3.7 – 5.4 mmHg greater increases in SBP for C4S compared to placebo are less than the mean increases reported by Shah et al. (> 6 mmHg). In contrast to BP, HR decreased from baseline to post-drink in the C4S condition. The reported effects of acute energy drink consumption on HR are less than conclusive (78), with studies showing an increase (33, 79) or no change (34, 80) in HR following acute energy drink consumption. However, our results are congruent with and may be explained by those of Cansev et al. (81), who demonstrated that administration of CDP-choline increased SBP and decreased HR in a dose-dependent manner *via* peripheral cholinergic and adrenergic signaling. The RPP, which is the product of SBP and HR, is a reliable and commonly used correlate of myocardial oxygen demand (82, 83), and an RPP threshold of 10,000 bpm·mmHg is often used to denote elevated cardiovascular risk (84). RPP was greater in C4S than placebo at all timepoints including at baseline, but RPP did not increase above baseline and remained below 9,000 bpm·mmHg in both the C4S and PLA conditions. While it is currently unclear whether the less dramatic effects on BP than previously reported are due to the specific C4S formulation, it is plausible based on prior evidence that the unique combination of green-tea extracted caffeine and CDP-choline in C4S may be responsible for these unique cardiovascular effects. This hypothesis is worth exploring in future studies because it may have important implications for long-term cardiovascular safety. Future studies may also wish to examine whether single nucleotide polymorphisms in genes of enzymes involved in caffeine metabolism (e.g., CYP1A2 or ADORA2A) influence the cardiovascular effects of energy drink consumption given that initial data suggest these genes may influence the effects of caffeine on cardiometabolic outcomes (39, 85–87).

The heart rate corrected QT interval (QTc) is an indirect measure of ventricular repolarization (88). Prolongation of

the QTc is a well-recognized clinical indicator of risk for ventricular arrhythmias. In this study, acute C4S consumption showed no effect on QTc, These results are congruent with those observed by Steinke et al. (33) and Brothers et al. (78), who reported no effects of either energy drink (100 – 240 mg caffeine) or coffee consumption on the QTc. In contrast, Shah et al. (37) observed significant QTc prolongation following acute consumption of two high-dose caffeine (304-320 mg), multi-ingredient energy drinks. However, as noted by Winniford (89) and Basrai (38), it does not appear that caffeine alone is responsible for this effect. In support, greater QTc prolongation and SBP increases have been reported following high-volume energy drink (32 oz) consumption than caffeine consumption alone when matched for caffeine dose (320 mg caffeine) (36). Overall, this literature suggests potential interactive effects of high-dose caffeine and other common energy drink ingredients on the QTc, again highlighting the formulation specific effects of energy drinks and the importance of studying the cardiovascular risk profile of each drink. Our findings indicate that the dosage and ingredient profile of C4S do not promote QTc prolongation.

In conclusion, our data suggest that acute C4S consumption produces robust improvements in cognitive function and mood that are accompanied by improvements in video game performance whereby success is highly dependent upon a player's visuospatial working memory (e.g., Tetris). Further, whereas C4S consumption produced moderate increases in systolic and diastolic blood pressures, it did not adversely affect myocardial oxygen demand or ventricular repolarization. Finally, there were no differences in reported adverse events between C4S and placebo. Together, our data support that acute C4S consumption produces nootropic effects that may translate to improved performance in cognitively demanding tasks with a satisfactory cardiovascular safety profile.

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Disclosure statement

As of August 8, 2022, Chris Lockwood (CML) was employed as Vice President of Scientific Affairs for Nutrabolt® (Austin, TX). CML's employment at Nutrabolt® began following completion of this study, which included data collection, analyses, and interpretation and completion of the primary manuscript draft. No other authors have competing interests to declare that are relevant to the content of this article.

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Authors contributions

LES and NDMJ wrote the original draft of this manuscript. LES, NDMJ, NFB, EMR, NJH, JPA, SLS, and CML reviewed and edited this manuscript. Study conceptualization and methodologies were carried out by CML and NDMJ. Data curation and investigation were performed by LES, NDMJ, NJH, JPA, and SLS. Data analyses were performed by LES and NDMJ. Funding was acquired by CML and NDMJ and beverages were acquired by CML. Project administration and supervision were managed by LES, NDMJ, and CML. All other resources were provided by NDMJ. Analytical validation was overseen by CML.

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