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Improvements in Concentration, Working Memory, and Sustained Attention Following Consumption of a Natural Citicoline-Caffeine Beverage

Steven E. Bruce, **Kimberly B. Werner**, **Brittany F. Preston**, and **Laurie M. Baker**

University of Missouri St. Louis

Abstract

The present study examined the neurocognitive and electrophysiological effects of a citicoline-caffeine-based beverage in 60 healthy adult participants enrolled in a randomized, double-blind, placebo-controlled trial. Measures of electrical brain activity using electroencephalogram (EEG) and neuropsychological measures examining attention, concentration, and reaction time were administered. Compared to placebo, participants receiving the citicoline-caffeine beverage exhibited significantly faster maze learning times and reaction times on a continuous performance test, fewer errors in a Go No-Go task, and better accuracy on a measure of information processing speed. EEG results examining P450 event related potentials (ERP) revealed that participants receiving the citicoline-caffeine beverage exhibited higher P450 amplitudes than controls, suggesting an increase in sustained attention. Overall, these findings suggest that the beverage significantly improved sustained attention, cognitive effort, and reaction times in healthy adults. Evidence of improved P450 amplitude indicates a general improvement in the ability to accommodate new and relevant information within working memory and overall enhanced brain activation.

Keywords

citicoline; EEG; nutrition; attention; functional beverage

The present study examined the neurocognitive effects of a citicoline-caffeine beverage. Citicoline, comprised of the combination of cytdine and choline, is a safe and well-tolerated compound that has been shown to increase the levels of choline in the brain and have no adverse systemic cholinergic effects (Conant & Schauss, 2004; Cotroneo et al., 2013; Rossi & Zanardi, 1993; Secades, 2011; Secades & Lorenzo, 2006). In addition to the documented improvements of caffeine on attention and neurocognitive functioning (Einother and Giesbrecht, 2013), choline is important for overall brain health and has been shown to reduce the risk of dementia, stroke and normal age- related memory loss (Gatti et al., 1992; Silveri et al., 2008). Zhang et al. (2013) conclude that substances such as caffeine and

Correspondence should be addressed to: Steven E. Bruce, Ph.D., University of Missouri-St. Louis, One University Boulevard, St. Louis, MO 63121-4499, 314-516-7204, 314-516-7233 (fax), brucese@umsl.edu.

Declaration of interest:

The authors report no conflicts of interest.

citicoline may play a role in improving memory performance by increasing expression of Na^+, K^+-ATPase, a sodium-potassium pump enzyme, which appears to play a role in the expression of Alzheimer's disease. Given the increasing prevalence of the aging population and general consumer interest in health-related products to enhance cognitive performance, it is important to identify the efficacy of consumer products formulated to enhance cognitive function.

A previous investigation identified improvements in attention and mental alertness 30 minutes following consumption of a beverage containing citicoline and caffeine (Bruce, 2012). Specifically, individuals receiving the citicoline-caffeine drink showed significant improvements in attention as measured by event-related potentials (ERP) and electroencephalogram (EEG) in healthy individuals. While encouraging, this study was the first to examine the specific ingredients together, the findings were limited to a small sample size, and their was an absence of neuropsychological tests examining working memory and problem solving skills (Bruce, 2012).

Administration of neuropsychological measures serves an important purpose in establishing the efficacy of health-related consumer products targeting brain function. While electrophysiological indices of brain enhancement provide a biological signal of efficacy, improvement in behavioral function remains the gold standard for demonstration of relevant functional impact. For example, tests such as continuous performance tests (CPT) are effective tools for evaluating sustained working memory, attention/vigilance, and arguably impulse control as previous research supports CPT ability to identify cognitive dysfunction and attentional impairment (Riccio, Reynolds, Lowe, & Moore, 2002). Research utilizing varying versions of the CPT have investigated alterations in cognitive performance after using stimulants (Riccio, Waldrop, Reynolds & Lowe, 2001) and displayed modulation of attention in individuals with neurological and psychological impairments including but not limited to Alzheimer's disease (Perry & Hodges, 1999), neurologic insult (Riccio et al., 2002), and childhood attention-deficit/hyperactivity disorder (ADHD; Huang-Pollock, Karalunas, Tam, & Moore, 2012).

In addition to CPTs, maze learning is a useful measure of visuospatial learning and memory and executive functioning (Barker, 1931; Walsh, 1994). Milner (1965) observed deficits in maze learning in individuals with temporal lesions that extended into the hippocampus. More recently, the Austin Maze, has been correlated with tests of visuospatial ability and memory, with visuospatial abilities contributing more on earlier attempts, while the participant was orienting themselves to the maze, and visuospatial memory contributing more on later attempts (Crowe et al., 1999). In addition to deficits in individuals with temporal lesions, Milner (1965) observed deficits in those with frontal lesions, suggesting the maze is also a measure of executive function. A recent study examining performance on the Austin maze in patients with temporal lobe epilepsy (TLE) indicated that performance on the Austin Maze correlated with measures of visuospatial ability in those with right TLE and with measures of executive function and memory in those with left TLE suggesting a lateralization of functions associated with maze performance (Hocking et al., 2013).

Event-related potentials (ERPs) are also a useful method to assess cognitive activation. ERPs allow for concurrent assessment of neurological activation across a number of cortical regions over time. ERP P450, as used in the current study, refers to a positive deflection in the ERP occurring around 450ms after stimulus presentation and has been established as an indicator of working memory updating (Clark, Orr, Wright, & Weber, 1998; Keage et al., 2008). Differences in P450 amplitude indicate a general change in the ability to accommodate new and relevant information within working memory (Keage et al., 2008). Several studies have identified P450 as a potential biomarker to differentiate individuals with and without Attention Deficit Hyperactivity Disorder (ADHD; Hermens et al., 2005; Mangina, Beuzeron-Mangina, & Grizenko, 2000; Williams et al., 2010). In a study of adolescents with ADHD, Mangina and colleagues (2000) found that ERP 450 amplitudes to a memory workload paradigm in pre-frontal and frontal brain regions distinguished healthy controls from an ADHD sample.

In the present study, we utilized EEG and neuropsychological tests that have been shown to measure performance in working memory, attention, and problem solving, as well as ERP's to examine brain activity. We predicted that participants that consumed the citicoline-caffeine beverage would show greater attention, improved working memory, and increased brain activation as measured by ERP 450s compared to those randomized to the placebo condition.

Method

Participants

Sixty healthy participants (27 men and 33 women) aged 20–40 (M = 24.2 years) were recruited for this double-blind randomized study. Of the 60 participants, 34 self-identified as "Caucasian", 14 as "Black" 6 as "Asian", 1 "American Indian" and five participants self-identified as "Other." The average years of education was 15.73 (SD = 1.42). Thirty participants were randomized to receive the citicoline-caffeine drink and 30 were randomized to the placebo condition. No significant differences were found between the two experimental groups across age, gender, ethnicity, or years of education.

All participants included in the study completed written informed consent. Exclusion criteria included a minimum daily caffeine intake of 35 mg of caffeine (equivalent to one can of soda) and a maximum intake of 200 mg of caffeine per day: therefore excluding those who are both novel to and consume high levels of caffeine. Prior to testing, all participants had refrained from caffeine for at least 6 hours. Additional exclusion criteria included a history of: (1) physical brain injury defined by loss of consciousness lasting more than 30 min; (2) brain tumor or stroke; (3) any medical condition that might put them at an increased risk if exposed to caffeine (including cardiac rhythm disorder, prior myocardial infarction, angina, congestive heart failure, hypertension, active peptic ulcer; all unlikely in the target demographic); (4) severe impediment to vision, hearing and/or hand movement; (5) addiction to illicit drugs; (6) current illicit substance use of any amount; (7) participants who are smokers (or who have smoked/used nicotine products within the 6 months prior to study entry); and (8) participants who consume two or more standard alcoholic drinks per day.

Experimental design

A double-blind, placebo-controlled experimental design was utilized in the current investigation. The study design was approved by a university institutional review board. Participants were randomized to receive either placebo or the citicoline-caffeine beverage containing the active ingredients prior to their arrival. The placebo condition was identical in quantity (11.5-ounces), carbohydrates (sugars) and flavor of the supplement drink minus the active ingredients (choline and citicoline (Cognizin), and caffeine). Measures of electrical brain activity using EEG were collected 30 min after consuming the beverage.

Procedure

Participants underwent a non-invasive EEG. The brain measures, using recording discs placed on the scalp during resting and a range of neurocognitive tasks (ERPs), enable an examination of automatic information processing over a fraction of a second. The experimental activation tasks were designed to examine the core adaptive competencies and underlying neural networks of the brain. The total battery took approximately 45 minutes to complete. Participants were seated in a sound and light attenuated room, set with an air-conditioned ambient temperature of 24 - 18C. An electrode cap (Quikcap) was used to acquire data from Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, FC3, FCz, FC4, T3, T4, T5, T6, Pz, P3, P4, O1, O2 and Oz electrode sites (32 channels; Compumedics Neuroscan Nuamps; 10–20 International System). Horizontal eye movement potentials were recorded using two electrodes, placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movement potentials were recorded using two electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid. Gratton procedure and electro-oculogram (EOG) thresholding for contaminated epochs (exceeding ^100 *m*V) allowed correction/rejection. The sampling rate was 500 Hz and a 70 Hz low-pass filter was applied to the signals before digitization.

Measures

Neuropsychological assessment tasks were utilized to assess cognitive alterations associated with consumption of the citicoline-caffeine beverage to assess improvements in working memory, attention, behavioral inhibition, and executive functioning.

Continuous Performance Task (CPT)

CPTs are effective tools for evaluating sustained working memory, attention/vigilance, and arguably impulse control (Riccio, Reynolds, Lowe, & Moore, 2002). The CPT paradigm utilized in the current study involves the identification of letter repeats that occur periodically during the task. The CPT requires discrimination between target letters and periodically displayed consecutive letter repeats, which are the target stimuli, and has been utilized to test sustained and selective attention. Participants were presented with a series of letters (B, C, D, or G) on the computer screen in white Arial font on a black background for 200ms with an inter-stimulus interval of 2.5 seconds (as developed and described in Williams et al., 2010). Participants were asked to respond by pressing buttons with the index finger of both hands simultaneously if the same letter appeared twice in a row. The paradigm consisted of 125 total stimuli presented in a pseudorandom order to ensure there

were no unintended repeat or repeated checkerboards: 85 non-target stimuli, 20 target stimuli in which the same letter was presented twice in a row, and 20 checkerboard stimuli. Participants were asked to ignore checkerboard stimuli during the instructions. The importance of both accuracy and speed of each response were outlined prior to the task. Participants completed a short practice trial prior to the actual test, which lasted approximately 8 minutes.

Austin Maze

Performance on the Austin Maze has been correlated with tests of visuospatial ability and memory, with visuospatial abilities contributing more on earlier attempts, while the participant was orienting themselves to the maze, and visuospatial memory contributing more on later attempts (Crowe et al., 1999). The Austin Maze was administered in the current investigation as a measure of visuospatial ability, memory and executive function. A 10 × 10 grid of dots was presented through which the correct path had to be determined by trial and error. Using four buttons the participant navigated through the grid, receiving both visual and auditory feedback in the form of a green dot accompanied by a high tone for a correct move and a red dot accompanied by a low tone for an incorrect move. The task ended after two successful navigations through the maze or after 8 minutes, whichever came first.

Go/No-Go Task

A Go/No-Go task in which participants were required to respond to a stimulus and inhibit their response to an alternate stimulus was used in the current study to measure attention and behavioral inhibition. In this task the word “PRESS” appeared on the screen in either green or red ink for 250 ms. Participants were instructed to press response buttons with the index fingers of both hands as quickly as possible only when the word appeared in green ink. This task lasted seven minutes and has demonstrated moderately high test-retest reliability ($r = .65$;$p < .001$) for commission errors (Weafer, Baggott, & de Wit, 2013).

Digit Symbol Substitution

Complex attention was measured with the Digit Symbol Substitution (Wechsler, 1981) test. Visual scanning, sustained attention, visuomotor coordination and information-processing speed are all important for performance on this task (Lezak, Howieson, Bigler, & Tranel, 2012). In this test, rows containing small empty squares are paired with a randomly assigned number from one to nine. A key above these squares pairs each number with a specific symbol. The objective is to write in the empty boxes the symbol that matches the number. The participant is instructed to complete as many empty boxes as possible in 120 seconds.

Trail Making Test—Visual attention and task switching was assessed using the Trail Making Test. It consists of two parts (A & B) in which participants are asked to connect a series of 25 dots (letter and numbers) as fast as possible while still maintaining accuracy. It has been shown to provide information regarding processing speed, mental flexibility, and executive functioning (Arnett & Labovitz, 1995).

Results

Neuropsychological Results

In order to avoid distributional assumptions and small sample issues, we elected to use the Wilcoxon Mann Whitney U-test. Table 1 reports the means and standard deviations for the group differences across the neuropsychological tests conducted. Compared to the placebo condition, participants in the citicoline-caffeine group had significantly faster Maze completion time ($U = 280.50$, $p = .008$), and significantly faster Maze path learning time ($U = 282.50$, $p = .008$). On average, the citicoline-caffeine group completed the Maze in 134 seconds compared with 186 seconds for the placebo group. The number of mazes completed for mastery was also significantly lower in the citicoline-caffeine group ($U = 314.00$, $p = .028$).

Results from the continuous performance test (CPT) indicate that the citicoline-caffeine group had significantly faster reaction times ($U = 242.50$, $p = .001$) as well as significantly fewer false miss errors ($U = 258.50$, $p = .001$) than the placebo group (Table 1). For the digit symbol test, the citicoline-caffeine group had significantly higher number of correct responses compared to the placebo group (90 vs. 79; $U = 688.00$, $p = .008$). Finally, in the Go/No-Go test, results indicate that the citicoline-caffeine group had significantly fewer false miss errors than did the placebo group (.03 vs. 48 respectively; $U = 329.00$, $p = .006$). No significant differences in Trail-Making A and B completion time or errors made were found across the two groups.

ERP/EEG Results

We hypothesized that 30 minutes after consumption, participants in the citicoline-caffeine group would show greater attention, improved working memory, and increased brain activation as measured by event-related potentials (P450) than those that consumed placebo. EEG results examining P450 event related potentials (ERP) revealed that participants receiving the citicoline-caffeine based beverage exhibited higher P450 amplitudes than controls across multiple areas, specifically in the frontal and prefrontal brain areas, suggesting an increase in sustained attention and (Table 2).

Discussion

Consistent with previous literature, results from this study indicate that participants receiving the citicoline-caffeine beverage exhibited increased performance on tasks associated with mental alertness, attention, and working memory in problem solving compared to a placebo condition (Bruce, 2012). Specifically, the citicoline-caffeine group displayed significantly faster maze learning times, fewer false alarm errors in a Go No-Go task measuring sustained cognitive effort, faster reaction times on a continuous performance test, and better accuracy on a measure of visual spatial processing speed. Moreover, examination of ERP indices revealed significantly larger P450 amplitudes in the citicoline group, particularly in pre-frontal and frontal areas which have been associated with working memory and sustained attention (Hermens et al., 2005; Mangina, Beuzeron-Mangina, & Grizenko, 2000; Williams et al., 2010). Evidence of improved P450 amplitude indicates a

general improvement in the ability to accommodate new and relevant information within working memory and overall enhanced brain activity.

Results from this study are consistent with prior research that suggests citicoline may play a role in increasing attention and alertness (Babb et al., 2002; Bruce, 2012; Cotroneo et al., 2013; Silveri et al., 2008). Citicoline is a compound that consists of cytidine and choline. It has been shown to activate the biosynthesis of phospholipids (PDE) in neuronal membranes (Babb et al., 2002). Since PDE has been shown to decrease with age and be associated with cognitive memory loss, increase in this substance may improve overall cognitive skills. In a recent study examining mild cognitive impairment in 349 elderly patients, Cotroneo and colleagues (2013) found that the citicoline group showed improvement in mini mental state examination (MMSE) scores after 9 months, compared to the untreated group that showed significant MMSE declines over the same time period. Other investigators have also found that increases in PDE from citicoline supplements have led to improved memory in older adults (Babb et al., 2002). Silveri et al. (2008) conclude that citicoline may assist in reducing cognitive declines associated with aging.

In addition to citicoline, a voluminous body of research supports the biological effects of caffeine on attention and executive functioning. In a recent review of caffeine's effects on attention, Einother and Giesbrecht (2013) concluded that caffeine has substantial benefits in improving both simple and complex attention tasks. Recent functional magnetic resonance imaging (fMRI) studies have also shown beneficial results with respect to caffeine and attentional processes. In a study examining the effects of caffeine in a sample of 24 healthy elderly participants, Haller et al. (2013) found that acute caffeine intake increases activity level in specific brain regions associated with working memory. Koppelstatter et al. (2008) also found that caffeine increases fMRI signal changes in a network of brain areas associated with executive and attentional functions during working memory processes. Both caffeine and citicoline are substances that may play a role in improving memory performance by increasing expression of a sodium potassium pump enzyme (Na^+, K^+-ATPase), in which deficits have been associated with Alzheimer's disease (Zhang et al. (2013). As such, a possible synergistic effect of citicoline and caffeine may exist theoretically, but there is a lack of evidence currently to make this conclusion. Few studies of caffeine alone have integrated these electrophysiological markers and cognition in the same study using this dose of caffeine. As such, even if driven by caffeine alone, the literature provides new information regarding stimulant effects on multifaceted markers of brain function.

Conclusions

Results of the present study propose that 250 mg of citicoline, when combined with caffeine, results in significant improvements in measures of sustained attention and working memory. Limitations to this preliminary study include the possibility of random group differences and the use of a young adult sample. Studies with an older adult sample may assist in the generalizability of these findings to an aging population. Moreover, the specific effects of each of the ingredients alone (citicoline, caffeine) compared with the other active compounds in the beverage were not systematically examined and thus, discrimination the

single effects of each substance could not be ascertained. However, results suggest growing support that a citicoline-caffeine based beverage is associated with improvements in measures of attention and mental alertness.

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Table 1

Neuropsychological Results (citicoline-caffeine group vs. placebo control).

	Citicoline Supplement (*n* = 30)	**Placebo (*n* = 30)**
	Mean (*SD*)	**Mean (*SD*)**
Trails A Time (seconds)	23.36 (5.62)	24.98 (8.93)
Trails B Time (seconds)	53.21 (17.69)	58.30 (21.68)
Symbol Search # Correct **	89.91 (14.74)	79.00 (13.77)
CPT Reaction Time (ms)**	464.53 (98.97)	544.03 (99.23)
CPT Variability RT (ms)**	135.40 (92.75)	178.13 (82.44)
CPT False Alarm Errors **	.77 (1.01)	1.77 (4.49)
CPT False Miss Errors **	.53 (1.20)	2.06 (2.84)
Maze Trials Completed *	7.03 (2.24)	9.32 (4.77)
Maze Completion Time (seconds)**	133.93 (66.01)	186.45 (101.73)
Maze Path Learning Time (seconds)**	109.80 (60.88)	161.03 (97.52)
Maze Overrrun Errors	14.07 (7.91)	21.94 (32.22)
Maze Total Errors	30.40 (15.54)	50.42 (68.71)
Go-NoGo Reaction Time (ms)	287.37 (46.10)	272.46 (62.23)
Go-NoGo False Alarm Errors	1.67 (1.67)	2.09 (2.04)
Go-NoGo False Miss Errors**	.03 (.18)	.48 (.97)

* $p < .05$,

** $p < .01$

Table 2.

ERP P450 Amplitude Indices (citicoline-caffeine group vs. placebo control).

P450 Amplitudes	Citicoline Supplement (*n* = 30)	Placebo (*n* = 30)
	Mean (*SD*)	Mean (*SD*)
Fp1*	1.515 (4.807)	.006 (5.055)
Fp2	1.670 (5.065)	1.484 (5.613)
F7*	4.429 (3.262)	2.505 (3.851)
F3**	7.071 (4.124)	3.915 (4.790)
Fz**	7.477 (4.648)	4.132 (5.164)
F4**	7.160 (4.026)	3.917 (4.940)
F8	3.909 (3.612)	3.044 (3.720)
FC3**	8.774 (3.683)	5.202 (5.031)
FCz**	9.489 (4.637)	5.633 (5.583)
FC4**	8.917 (4.052)	4.956 (4.806)
T3**	6.117 (2.680)	3.268 (2.943)
C3**	10.020 (3.698)	6.510 (4.775)
Cz**	11.185 (4.457)	7.327 (5.560)
C4**	9.921 (3.798)	6.317 (5.265)
T4*	6.224 (2.714)	4.175 (3.963)
CP3*	10.545 (3.892)	7.556 (4.411)
CPz**	12.131 (4.051)	8.744 (5.109)
CP4*	10.623 (3.986)	7.668 (4.897)
T5	6.718 (2.816)	5.810 (3.373)
P3	10.051 (4.271)	8.112 (4.313)
Pz*	12.634 (4.087)	9.618 (4.828)
P4*	10.498 (4.534)	7.982 (4.176)
T6	6.093 (3.546)	5.686 (3.438)
O1	7.901 (3.700)	7.401 (4.113)
Oz	8.603 (3.467)	7.648 (4.770)
O2	8.137 (3.530)	7.655 (4.564)

* $p < .05$,

** $p < .01$