Article

The Effect of Citicoline Supplementation on Motor Speed and Attention in Adolescent Males

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Abstract

Objective: This study assessed the effects of citicoline, a nutraceutical, on attention, psychomotor function, and impulsivity in healthy adolescent males. **Method:** Seventy-five healthy adolescent males were randomly assigned to either the citicoline group (n = 51 with 250 or 500 mg citicoline) or placebo (n = 24). Participants completed the Ruff 2&7 Selective Attention Test, Finger Tap Test, and the Computerized Performance Test, Second Edition (CPT-II) at baseline and after 28 days of supplementation. **Results:** Individuals receiving citicoline exhibited improved attention (p = 0.02) and increased psychomotor speed (p = 0.03) compared with those receiving placebo. Higher weight-adjusted dose significantly predicted increased accuracy on an attention task (p = 0.01), improved signal detectability on a computerized attention task (p = 0.03), and decreased impulsivity (p = 0.01). **Discussion:** Adolescent males receiving 28 days of Cognizin® citicoline showed improved attention and psychomotor speed and reduced impulsivity compared to adolescent males who received placebo. *(J. of Att. Dis. XXXX; XX(X) XX-XX)*

Keywords

cognition, adolescents, cognitive enhancement, citicoline

Introduction

Citicoline (cytidine-5′-diphosphocoline or CDP-choline) is an organic molecule that is thought to influence cellular metabolism in the brain. It is an essential intermediary component of the synthesis of phosphatidylcholine, a major phospholipid in the brain that aids in neuronal membrane repair (Conant & Schauss, 2004; Secades, 2011), and also contributes to the synthesis of several essential neurotransmitters, including acetylcholine and dopamine (Saver, 2008; Secades, 2011). Citicoline has demonstrated cognitive-enhancing and neuroprotective properties in previous preclinical and clinical studies (Ozay et al., 2007; Parisi, Coppola, Centofanti, et al., 2008; Secades, 2011) and is marketed as a nutritional supplement in the United States. In addition, prior research on citicoline has shown very few side effects, although research thus far has focused primarily on adults (Clark, Wechsler, Sabounjian, & Schwiderski, 2001; Secades, 2011; Zafonte et al., 2009).

Oral supplementation of citicoline is metabolized into choline and uridine within the intestine and is rapidly absorbed, with waste excretion of less than 1% as demonstrated by pharmokinetic studies (Wurtman, Regan, Ulus, & Yu, 2000) . These compounds are distributed throughout the body via general circulation and are utilized in a variety of biosynthetic pathways. In particular, uridine crosses the blood–brain barrier and is synthesized into uridine-5′-triphosphate, which is then metabolized into cytidine triphosphate and CDP-choline (Wurtman, Regan, Ulus, & Yu, 2000). A clinical study measuring in vivo brain chemistry through proton magnetic resonance spectroscopy (MRS) revealed increased plasma choline in young adults (with a mean age of 25) 3 hr after oral supplementation of citicoline (Babb, Appelmans, Renshaw, Wurtman, & Cohen, 1996).

Studies examining exogenous administration of citicoline have found influences in regional brain metabolism and increased dopamine synthesis in certain brain areas (Secades, 2011). A study by Silveri and colleagues used phosphorus MRS to investigate changes in brain metabolism after citicoline supplementation of either 500 or 2,000 mg/day for 6 weeks. The authors noted improved bioenergetics and enhanced phospholipid membrane maintenance in the frontal lobe (Silveri et al., 2008). Frontosubcortical

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pathways thought to control attention and motor behavior involve several neurotransmitters, including dopamine (Faraone & Biederman, 1998; Levy & Swanson, 2001). Citicoline may increase dopamine synthesis through enhancing tyrosine hydroxylase activity, which inhibits dopamine reuptake at the synapse (Saver, 2008). An animal study of exogenous citicoline administration for 28 days to rats demonstrated increased dopamine release in the striatum (Agut, Ortiz, & Wurtman, 2000). Considering that dopamine is involved in various functions, including movement and attention (Saver, 2008), and that previous studies have found relations between frontal lobe cognitive function and striatal dopamine processing (Braskie et al., 2008), citicoline may be a promising candidate for improving motor and attentional abilities.

Animal studies of stroke and traumatic brain injury in rats have found significantly improved motor function shortly after exogenous administration of 100 mg/kg (Diederich et al., 2012) and 300 mg/kg of citicoline (Cakir et al., 2005). In addition, a study by Drago and colleagues (1993) demonstrated improved motor capacity and coordination after supplementation of 10 to 20 mg/kg/day for 20 days in rats bred for cognitive and motor deficits, as well as in rats with drug-induced behavioral changes. In clinical trials investigating treatment of individuals with head injury, Calatayud Maldonado, Calatayud Perez, and Aso Escario (1991) demonstrated that a mean dose of 4 g/day tapering off to 600 mg/day led to recovery of motor disorders and higher neurological functions. Additional studies have found citicoline supplementation to result in improved motor function in various conditions, including cerebral infarction, Parkinson's disease, and head injuries (Secades, 2011).

Citicoline also has demonstrated a positive impact on attention. A study by Alvarez-Sabin and colleagues (2013) investigating neurocognitive decline following an initial stroke in humans showed citicoline supplementation of 1g/day for 12 months resulted in improvement of attention and executive function. Additional studies have demonstrated improved attention in various conditions, including old age, chronic cerebral vascular disease, and alcohol withdrawal after citicoline dosing (Secades, 2011). Evidence also suggests that citicoline may increase visual attentional abilities. Dopamine is involved in post-retinal visual pathways (Brandies & Yehuda, 2008) and may mediate control of visual cortical signals by the prefrontal cortex (Noudoost & Moore, 2011). Animal studies indicate that citicoline increases retinal concentration of dopamine (Noudoost & Moore, 2011). In studies of children with amblyopia and other visual impairments, citicoline doses ranging from 250 to 1,000 mg/day have been shown to increase visual acuity (Pawar, Mumbare, Patil, & Ramakrishnan, 2014; Siddiqui, Lennerstrand, Pansell, & Rydberg, 2012). In addition, in patients with glaucoma and non-arteritic ischemic optical neuropathy, citicoline supplementation of 1,600 mg/day for two 60-day periods improved visual function in one clinical trial. The authors suggest that citicoline may facilitate increases in dopamine, thereby contributing to improvements in the visual field through increasing attentional ability (Parisi, Coppola, Centofanti, et al., 2008; Parisi, Coppola, Ziccardi, Gallinaro, & Falsini, 2008). Collectively, these studies demonstrate citicoline's contribution to improved attention and visual ability, potentially mediated by increasing dopamine levels.

Fewer investigations have been conducted on the effects of citicoline on motor and cognitive enhancement in normative populations. A study by McGlade and colleagues (2012) examining citicoline supplementation of 250 and 500 mg/day for 28 days found improved attention performance and reduced impulsivity in healthy adult women. To our knowledge, the present study is the first to investigate the effects of citicoline administration in healthy adolescent males. Considering the frontal lobes are among the last brain regions to mature and do not reach full adult capacity until the mid-20s (Rubia et al., 2000), citicoline may support maximal functioning in areas not yet fully developed in adolescents.

Several studies investigating citicoline supplementation also have accounted for the participants' developmental stage by using varying doses depending on developmental factors. One study used either a high (1,200 mg/day) or low (800 mg/day) dose based on body weight (Fresina, Dickmann, Salerni, De Gregorio, & Campos, 2008), and another used age as a cutoff between two doses (250 mg/day for children below 5 years of age, 500 mg/day for children over 5 years old). Despite the contribution of these studies, there is relatively little data on the pharmacokinetics of citicoline at various developmental stages. Although both age and body weight may be important considerations, these variables are generally highly correlated in children (Pawar et al., 2014), and body weight may have a greater influence on pharmacokinetics and drug metabolism.

The current study used a double-blind, placebo-controlled, three-arm design to investigate the effectiveness of two doses of citicoline (250 and 500 mg/day) or placebo on attention and motor function after 4 weeks of supplementation. Healthy adolescent males were given neuropsychological measures assessing motor performance and attention at the beginning and end of the study period to investigate changes in functioning. The study population was limited to males to decrease heterogeneity in light of sex differences in brain maturation during adolescence (De Bellis et al., 2001). The safety guidelines of the United States Food and Drug Administration (FDA) regarding pharmaceutical clinical trials were followed, and side effect profiles were tracked for each participant. Adolescent males who received citicoline were hypothesized to demonstrate improved motor and attentional performance on neuropsychological tasks compared with adolescent males who received placebo.

Table 1. Reasons for Screen Failures.

Reasons for screen failures	*n*	Total %[a]
Prior psychiatric diagnosis	3	3
Taking medications	3	3
Older than age cutoff	3	3
Female	1	1
Out of area during study	1	1
Did not return calls	1	1
Parent refused child participation	1	1
No reason given	4	4
Total screened	108	—
Total screen failures	17	16

[a]Percentage of the total screened.

Table 2. Participant Enrollment Status.

Participant enrollment status	*n*
Enrolled	83
Completed[a]	75
Discontinued from study—Incompletes[b]	
DSM Axis I diagnosis	2
Abnormal baseline medical panel	1
Non-compliance with dosing	5

Note. DSM = Diagnostic and Statistical Manual of Mental Disorders.
[a]Completed both visits and used for final analysis.
[b]Discontinued from study: Will not be used for final data analysis.

Participants and Method

Participants

Eighty-three healthy male adolescents ranging from 13 to 18 years of age ($M = 15.52$, $SD = 1.66$) were recruited from Salt Lake City, Utah, and 75 healthy male adolescents completed the study. Recruitment for participants was initiated with fliers in the Salt Lake City area, then subsequently by word of mouth. Study participants were screened by telephone prior to study enrollment to ensure they met the inclusion criteria for the study. No exclusions were made based on ethnicity. Potential participants were enrolled if they had no significant medical conditions, no history of comorbid psychiatric disorder, current Axis I or II diagnosis, and no history of previous participation in a pharmacotherapeutic trial. They were excluded if they had a history of head injury with loss of consciousness of more than 5 min and/or had taken psychotropic medication (see Tables 1 and 2 for participant exclusions). The study was conducted under the guidelines of the University of Utah Institutional Review Board (IRB). All participants provided written informed consent per the IRB and Declaration of Helsinki. Study participants began the study by reviewing and signing the consent form with a research assistant. Participants below the age of 18 were provided with assent forms and their parents signed the consent form. Participants were compensated financially for their time.

Study Design

At the baseline visit, participants who screened positive for study entry completed a structured diagnostic interview (Kiddie Schedule for Affective Disorders and Schizophrenia [K-SADS]) to assess for Axis I psychiatric diagnoses including ADHD, standard symptom measures, and self-rating questionnaires assessing mood, sleep, complexion, and appetite. Participants also completed a medical exam. Specifically, they provided a urine sample for drug screening and a blood sample for comprehensive chemistry panel (sodium, potassium, chloride, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphorus), liver function tests (serum glutamic oxaloeacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), gamma-glutamyl transpeptidase (GGT), total bilirubin, albumin), and a full blood count (white blood cell count (WBC), red blood cell count (RBC), platelet count). A visual acuity test was given in addition to weight and height measurements.

Participants also completed a neurocognitive battery including the Wechsler Adult Intelligence Scale–Revised (WASI-R) to assess intelligence (i.e., IQ) in addition to measures of attention and motor speed (Finger Tap Test, Ruff 2&7 Selective Attention Test, and the Computerized Performance Test, Second Edition [CPT-II]). Although no participants met criteria for a psychiatric disorder at enrollment, symptom assessments were still completed throughout the study to evaluate changes in mood state. In addition, self-reports of sleep habits, lifestyle, and exercise routines were also administered at baseline as well as at each study visit to assess changes in health habits during study participation.

Following completion of the baseline assessment, participants who met inclusion criteria including not meeting diagnostic criteria for any Axis I disorders were randomly assigned to 250 mg citicoline, 500 mg citicoline, or placebo group and given a 28-day supply of oral citicoline (Cognizin® KYOWA HAKKO BIO CO., LTD., Japan) or placebo. Both participants and researchers were blind to the treatment condition during data collection. Participants were instructed to take one capsule a day every day for the next 28 days. Participants returned for a visit on the 28th day of their study participation. The pill bottle and the dosage calendar were collected from each participant. Urine and blood were again obtained. Participants also completed symptom and neuropsychological measures that were similar to those given during the baseline visit, including the Finger Tap Test, the Ruff 2&7, and the CPT-II. Finally, participants were given the Monitoring of Side Effects Scale (MOSES) to measure potential side effects of citicoline supplementation.

Table 3. Baseline Demographic Characteristics—Between-Group Differences.

	Treatment (n = 51)	Placebo (n = 24)	p
Age ± *SD*	15.41 ± 1.70	15.71 ± 1.73	0.98
Education (years) ± *SD*	9.00 ± 1.76	9.42 ± 1.82	0.48
Height (cm) ± *SD*	171.14 ± 9.24	171.95 ± 10.76	0.64
Weight (kg) ± *SD*	61.74 ± 14.80	62.90 ± 14.34	0.82
IQ (WASI) ± *SD*	106.04 ± 10.33	107.33 ± 9.50	0.45

Note. WASI = Wechsler Adult Intelligence Scale.

Measures

The Finger Tap Test has been supported as a reliable measure of motor speed and control (Reitan & Wolfson, 1985). It is a common assessment measure administered by neuropsychologists to detect cognitive and motor impairment. During the Finger Tap Test, the participant is instructed to use his index finger to press a lever attached to a mechanical counter as many times as he can within the designated time period. The participant is instructed to move only his index finger, not the entire hand. The same process is completed using the index finger of the dominant and the non-dominant hand. The Finger Tap Test was administered at the baseline visit and after 28 days of supplementation.

The Ruff 2&7 Selective Attention Test is a reliable assessment for measuring two aspects of visual attention: sustained attention and selective attention (Ruff & Allen, 1996). This test is a timed cancellation task with a series of 20 trials involving visual searching. The respondent detects and marks through all given stimuli the digits "2" and "7" embedded in blocks of distractor numbers or letters. Both speed and accuracy on the search task are calculated. The Ruff 2&7 was administered at the baseline visit and after 28 days of supplementation.

The Computerized Performance Test, Second Edition (CPT-II) is a computerized test designed to measure sustained attention as well as impulsivity (Conners, Epstein, Angold, & Klaric, 2003; Epstein et al., 2003). The test requires participants to attend to a series of target and distracter stimuli for a 14-min duration, beginning with a short practice test. Participants are required to respond as quickly and accurately as possible when the target letters appear on the computer screen by pressing the spacebar. Outcome variables include commission errors, which is the number of times the participant incorrectly responded to a stimuli (i.e., a measure of impulsivity) and detectability (i.e., a measure of ability to detect stimuli requiring responses from extraneous stimuli).

The MOSES is a measure designed to assess common symptoms or adverse events associated with psychopharmacological medications (Kalachnik, 1999). This scale is divided into nine body areas representing a typical physical examination. The interviewer asks participants whether they have each symptom on the measure and, if so, asks them to report the level of severity of the symptom on a scale from 0 (*not present*) to 4 (*severe*). This scale was administered after 28 days of supplementation to assess presence or absence of side effects. Severity ratings for each side effect reported by the participant were totaled to create a summary score for each individual.

Statistical Analysis

Between-group ANCOVAs were run in SPSS (IBM Statistics 2.0) to assess side effect profiles and differences in day 28 neuropsychological scores. In light of the large range of weights in our participant sample (from 38 to 104 kg) and the wide range of pubertal timing in boys in adolescence (Rogol, Clark, & Roemmich, 2000), we also performed weight-adjusted dose analyses in SPSS (IBM Statistics 2.0) of the Day 28 neuropsychological scores.

Results

Seventy-five healthy male adolescents participated in the study. Eight additional participants enrolled in the study but did not complete the study due to study-unrelated events. The 75 participants were divided into three groups of approximately equal sizes (250 mg: n = 27; 500 mg: n = 24; placebo: n = 24). One group took the low dose of 250 mg/day, one group took the high dose of 500 mg/day, and one group took a placebo for 28 days. Groups receiving citicoline were collapsed into a single treatment group so that comparisons could be conducted between the treatment and placebo groups.

Between-group analyses prior to supplementation revealed no group difference on estimated IQ as measured by the WASI-R (p = 0.61). Mean estimated IQs for each group were within the average range (treatment = 106.04, placebo = 107.33; see Table 3). In addition, there were no between-group differences at baseline on other neurocognitive assessment measures, including Finger Tap Total Dominant Hand (FTDH), Finger Tap Total Non-Dominant Hand (FTNDH), Ruff 2&7 Speed, Ruff 2&7 Accuracy, CPT-II Detectability, and CPT-II Commission Errors (p's = 0.17-0.68).

Table 4. Treatment Group Compared With Placebo: FTDH and FTNDH at Baseline Visit and After 28 Days of Supplementation.

	Baseline	28th day	*p*
FTDH			
Treatment (*n* = 51)	479.96 + 69.39	518.05 + 49.86	0.03
Placebo (*n* = 24)	504.90 + 81.08	513.43 + 64.03	
FTNDH			
Treatment (*n* = 51)	446.95 + 70.57	470.52 + 60.08	0.62
Placebo (*n* = 24)	456.78 + 56.60	473.41 + 57.02	

Note. FTDH = Finger Tap Total Dominant Hand; FTNDH = Finger Tap Total Non-Dominant Hand.

Table 5. Treatment Group Compared With Placebo: Ruff 2&7 Speed and Ruff 2&7 Accuracy Tasks at Baseline Visit and After 28 Days of Supplementation.

	Baseline	28th day	*p*
Ruff 2&7 Speed			
Treatment (*n* = 51)	86.98 ± 22.62	104.90 ± 21.31	0.03
Placebo (*n* = 24)	84.04 ± 16.93	96.79 ± 19.56	
Ruff 2&7 Accuracy			
Treatment (*n* = 51)	90.88 ± 17.14	103.06 ± 15.51	0.86
Placebo (*n* = 24)	89.04 ± 19.51	102.75 ± 16.01	

Neurocognitive Assessment

Analyses of Finger Tap Test and Ruff 2&7 performance results from baseline and Day 28 were performed with SPSS (IBM Statistics 20.0). All *p* values are reported as one-tailed because a priori hypotheses specified improvement on scores after supplementation.

Between Group Comparisons for Day 28 Neuropsychological Scores

ANCOVAs were run to examine differences between treatment and placebo groups on FTDH and FTNDH, as well as on the Ruff 2&7 Speed and Accuracy Tasks after 28 days of supplementation (Tables 4 and 5). Performance at the baseline visit (FTDH, FTNDH, Ruff 2&7 Speed, and Ruff 2&7 Accuracy, respectively) was included as covariates to account for baseline performance. Between-group differences showed that after 28 days of citicoline supplementation, individuals in the treatment group exhibited increased motor speed compared with individuals in the placebo group when using the dominant hand ($p = 0.03$; Figure 1). There were no between-group differences for the non-dominant hand ($p = 0.62$). In addition, individuals in the treatment group exhibited improved attention compared with the placebo group as demonstrated by increased performance on the Ruff 2&7 Speed ($p = 0.02$; Figure 2). There were no between-group differences for Ruff 2&7 Accuracy ($p = 0.86$).

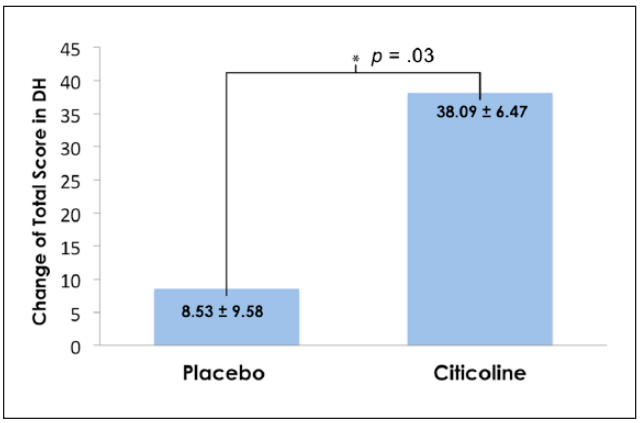

Figure 1. Improved performance on the Finger Tap Test after supplementation. * $p < 0.05$
Note. DH = Dominant Hand

Weight-Adjusted Dose Comparisons for Day 28 Scores

In light of the large range of weights in the participant sample (from 38 to 104 kg) and the wide range of pubertal timing in boys in adolescence (Rogol et al., 2000), weight was accounted for when analyzing the dose-related effects of citicoline. (See mean baseline and 28-day scores for the combined treatment group on each of the variables of interest in Table 6.) Within the treatment group, dosage (mg) of citicoline was divided by the weight of participants (kg) to

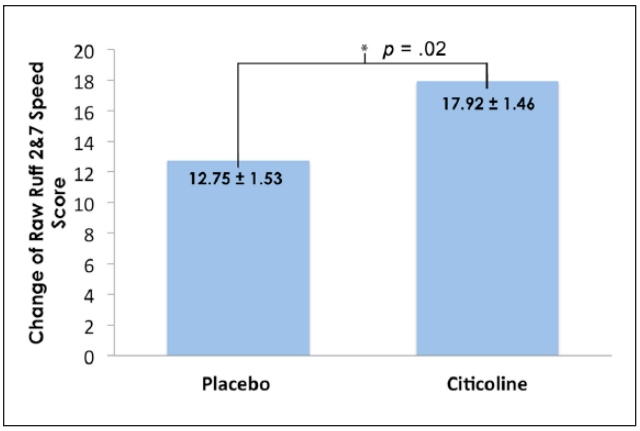

Figure 2. Improved performance on the Ruff 2&7 Speed task after supplementation.

Table 6. Raw Data for Treatment Group: Ruff 2&7 Accuracy, CPT-II Detectability, and CPT-II Commission Errors at Baseline Visit and After 28 Days of Supplementation.

	Baseline	28th day
Ruff 2&7 Accuracy (n = 51)	45.20 ± 8.57	51.53 ± 6.72
CPT-II Detectability (n = 51)	49.74 ± 11.45	45.05 ± 16.67
CPT-II Commission Errors (n = 51)	47.67 ± 10.73	44.68 ± 13.23

Note. CPT-II = Computerized Performance Test, Second Edition.

enable analyses based on weight-adjusted dose (mg/kg). Separate regressions were run for weight-adjusted dose predicting each of the following variables: the Ruff 2&7 Accuracy Score, the CPT-II Detectability score, and the CPT-II Commission Errors score (Table 7).

Results indicated that the weight-adjusted dose of citicoline significantly predicted change scores for Ruff 2&7 Accuracy, with greater improvement in accuracy (a higher *T*-score) for 28 days compared with baseline for higher weight-adjusted dose (p = 0.01; Figure 3). Likewise, weight-adjusted dose significantly predicted change scores for CPT-II Detectability, with greater improvement in detectability (a lower *T*-score) for 28 days compared with baseline for higher weight-adjusted dose (p = 0.03; Figure 4). Finally, weight-adjusted dose significantly predicted change scores for CPT-II Commission Errors, with greater improvement in commission errors (a lower *T*-score) for 28 days compared with baseline for higher weight-adjusted dose (p = 0.01; Figure 5).

Side Effect Profiles

There were no between-group differences between the placebo and treatment group in side effect profiles after 28 days of citicoline supplementation (M = 0.45 ± 1.53 vs. M = 0.73 ± 1.35, p = 0.46). Individual items are presented in Tables 8 to 10. Metabolic parameters were collected at baseline and at study completion to measure any differences in physiology and health status. No significant within-group differences were seen after supplementation except on creatinine, which was not found to be clinically significant. Interestingly, the placebo group showed a greater change on creatinine than the cognizin-supplemented group (see Table 11).

Discussion

In the current study, citicoline supplementation was associated with improved motor function and attentional abilities in healthy adolescent males. Performance on the Finger Tap Test and Ruff 2&7 was used to assess improvement across 28 days of administration. There were no differences in age, education, height, weight, or estimated levels of global cognitive function at baseline. Finally, no significant differences were demonstrated between side effect profiles for the treatment and placebo group after 28 days of citicoline supplementation. This is consistent with prior research focusing on adults that has shown few side effects associated with citicoline supplementation.

Previous studies support our findings of increased motor function and attentional abilities for a variety of conditions, including head injury, stroke, and neurocognitive decline following a stroke (Alvarez-Sabin et al., 2013; Calatayud Maldonado et al., 1991; Ozay et al., 2007). However, these studies have investigated citicoline supplementation within clinical populations, and few studies have investigated citicoline's effects in healthy individuals. Moreover, these studies examined improvement of *deficits* in motor and attentional abilities, whereas our study measured enhancement of abilities in individuals with normative functioning in the respective domains. By demonstrating enhancement effects in healthy adolescent males, our study broadens the literature on citicoline supplementation.

Similar to animal studies that support the use of low doses of citicoline (Cakir et al., 2005; Diederich et al., 2012), the current study demonstrates measurable effects in human populations using a relatively small dose of citicoline (250 up to 500 mg/day or up to approximately 6.6 mg/kg for an average adult) compared with amounts commonly used in clinical trials (1,000 mg/day or roughly 13.2 mg/kg for an average adult; Pawar et al., 2014). Specifically, this study provides behavioral evidence from between-group analyses as well as weight-adjusted dose analyses for improved frontal lobe function with low doses of citicoline, as reflected in enhanced attentional abilities. Furthermore, this study supports previous research demonstrating citicoline's effects on improving bioenergetics in the frontal lobe (Silveri et al., 2008). The frontal lobes are still maturing during adolescence (Rubia et al., 2000), and enhanced

Table 7. Dose by Weight Regressions: Predicting Change Scores for Ruff 2&7 Accuracy, CPT-II Detectability, and CPT-II Commission Errors.

	Ruff 2&7 Accuracy			CPT-II Detectability			CPT-II Commission Errors		
	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*
Dose by weight	0.35	2.61	0.01	−0.31	−2.27	0.03	−0.37	−2.78	0.01

Note. CPT-II = Computerized Performance Test, Second Edition.

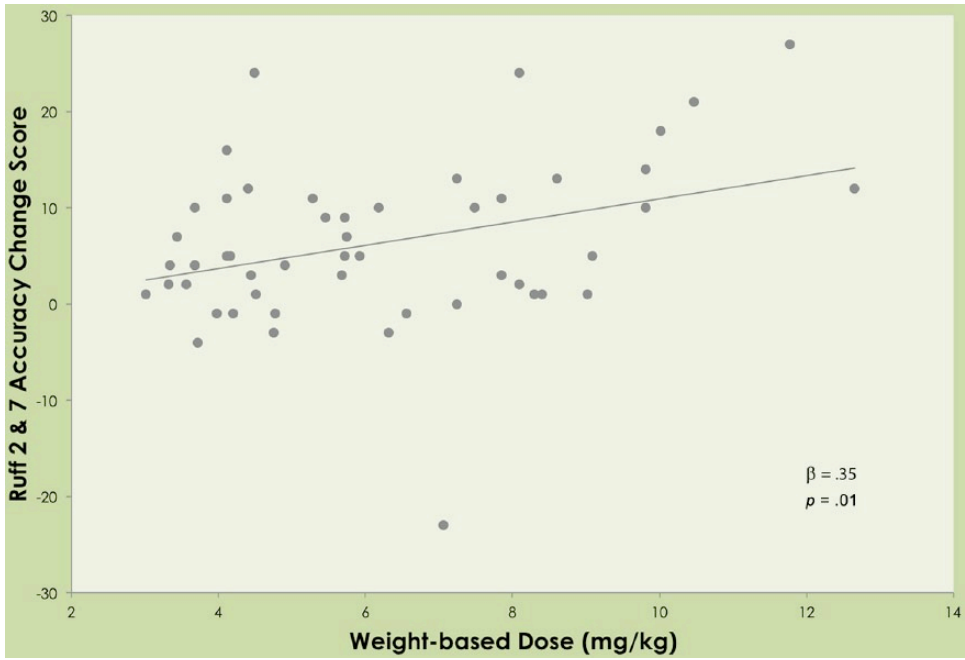

Figure 3. Dose by weight predicting Ruff 2&7 Accuracy change score (higher change score = more improvement).

visual selective attention, reduced impulsivity, and improved motor function may enable adolescents to remain on a healthy trajectory during a time in which there is significant neural development (Andersen, 2003) as well as increased risk-taking behavior (Volkow & Li, 2004).

Although we did not measure dopamine in this study, it is likely that citicoline administration may increase dopaminergic activity in healthy adolescent males and result in the changes observed in this study. Dopamine contributes to the functioning of the frontal lobe and plays a strong role in attention regulation (Nieoullon, 2002). In addition, the frontosubcortical pathways thought to control attention and motor behavior involve dopamine (Faraone & Biederman, 1998; Levy & Swanson, 2001), and previous studies have found relationships between striatal dopamine processing and frontal lobe cognitive function (Braskie et al., 2008). Dopaminergic uptake is related to motor abilities in disorders such as Parkinson's disease, as well as attentional performance reflecting frontal lobe function (Nieoullon, 2002; Rinne et al., 2000), and a study using positron emission tomography (PET) and dopamine receptor tracers demonstrated dopamine is released during tasks requiring attention, suggesting the prominent role of this neurotransmitter in regulating these abilities (Aalto, Bruck, Laine, Nagren, & Rinne, 2005). Citicoline has been shown in previous studies to increase levels of dopamine (Agut et al., 2000; Rejdak, Toczolowski, Solski, Duma, & Grieb, 2002), improve dopamine receptor function through increasing the number of receptors (Gimenez, Raich, & Aguilar, 1991), and to have a neuroprotective effect on dopaminergic neurons (Radad, Gille, Xiaojing, Durany, & Rausch, 2007). Increased bioavailability of dopamine may be one mechanism through which citicoline improves motor and attentional functions.

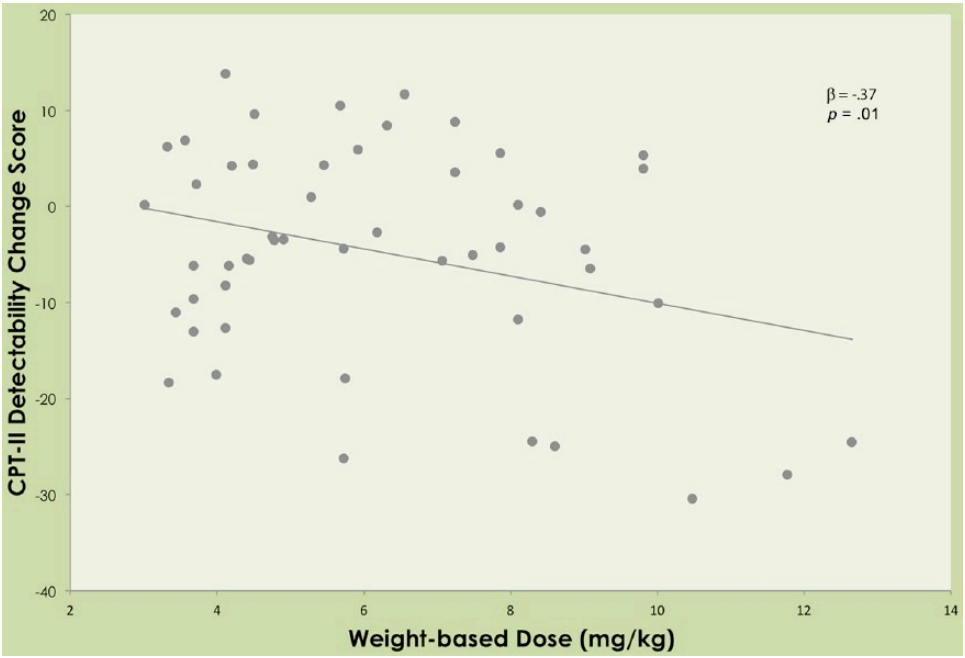

Figure 4. Dose by weight predicting CPT-II Detectability change score (lower change score = more improvement).
Note. CPT-II = Computerized Performance Test, Second Edition.

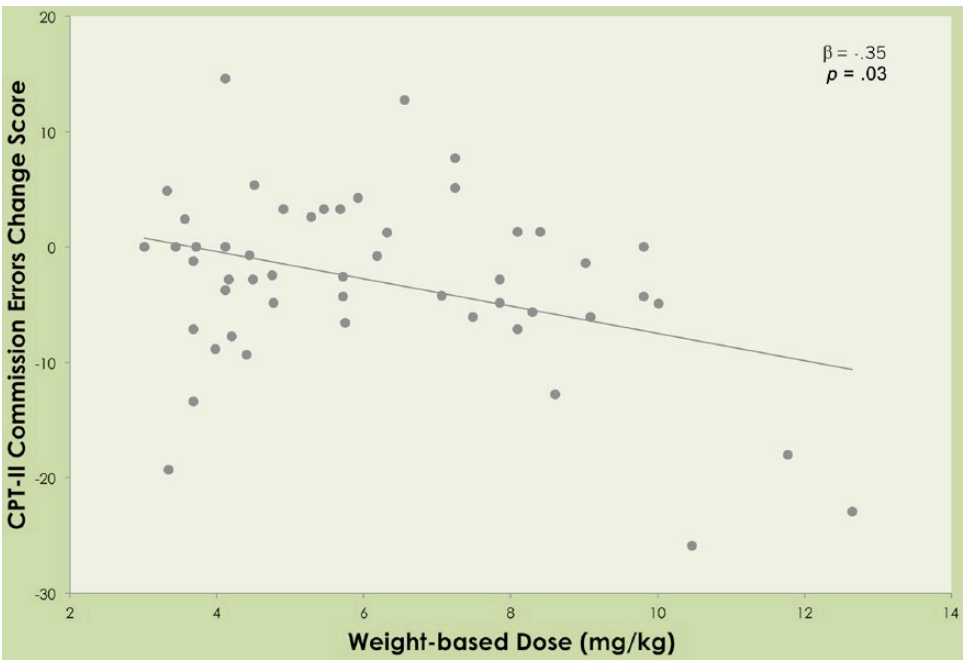

Figure 5. Dose by weight predicting CPT-II Commission Errors change score (lower change score = more improvement).
Note. CPT-II = Computerized Performance Test, Second Edition.

Table 8. Adverse Events by Body System and Severity.

Body system and preferred system	Total n[a]	Total %[b]	Severity
Overall	75	100	
Total participants reporting side effects	32	42.6	
Ears/eyes/head			
Headache	5	6.7	Minimal
	2	2.7	Mild
Blurred vision	1	1.3	Mild
Mouth			
Dry mouth	8	10.7	Minimal
	3	4.0	Mild
Slurred speech	3	4.0	Minimal
Drooling/pooling	1	1.3	Minimal
Nose/throat/chest			
Sore throat	3	4.0	Minimal
Runny nose	3	4.0	Minimal
Gastrointestinal			
Decreased appetite	1	1.3	Minimal
	1	1.3	Mild
Thirst increase	7	9.3	Minimal
	4	5.3	Mild
Diarrhea	3	4.0	Minimal
Abdominal pain	1	1.3	Minimal
Musculoskeletal/neurological			
Complaints of muscle sprain or aches	1	1.3	Minimal
Muscle tingling	2	2.7	Minimal
Fainting/dizziness upon standing	1	1.3	Minimal
Skin			
Rash	1	1.3	Minimal
Red/sunburn skin	1	1.3	Minimal
Dry/itchy skin	1	1.3	Minimal
Acne	3	4.0	Minimal
Psychological			
Vivid dreams	1	1.3	Mild
Drowsiness	3	4.0	Minimal
	2	2.7	Mild
Insomnia	1	1.3	Minimal
	1	1.3	Mild
Agitation	3	4.0	Minimal
	1	1.3	Mild
Irritability	3	4.0	Minimal
	1	1.3	Mild
Confusion	2	2.7	Minimal
Difficulty concentrating	1	1.3	Minimal
Aggression	1	1.3	Minimal

[a]Number of participants experiencing an adverse event (participant is counted only once for each adverse event).
[b]Percentage of total number of participants who completed both visits of the study (n = 75).

The sample size for the current study was modest with 75 adolescent males. Although smaller sample sizes can decrease power, there were still significant between-group differences on attention, psychomotor speed, and inhibition. Nonetheless, it would be beneficial to replicate the current study findings with more participants. In addition, future directions for research may include investigating effects of citicoline administration in healthy adolescent females and examining whether there are differences in effects. Notably, the study by McGlade and colleagues, which included exclusively females but at an older age (between 40 and 60 years old), found improved attentional

Table 9. Adverse Events by Body System and Severity, Separated by Dose (Number).

Body system and preferred system	500 mg[a]	250 mg[a]	Placebo[a]	Severity
Overall	24	27	24	
Total participants reporting side effects	10	13	9	
Ears/eyes/head				
Headache	2	2	1	Minimal
	1	1		Mild
Blurred vision		1		Mild
Mouth				
Dry mouth	3	3	2	Minimal
	1	1	1	Mild
Slurred speech	2	1		Minimal
Drooling/pooling		1		Minimal
Nose/throat/chest				
Sore throat			3	Minimal
Runny nose	1		2	Minimal
Gastrointestinal				
Decreased appetite		1		Minimal
		1		Mild
Thirst increase	2	3	2	Minimal
	2	2		Mild
Diarrhea	1	1	1	Minimal
Abdominal pain			1	Minimal
Musculoskeletal/neurological				
Complaints of muscle sprain or aches		1		Minimal
Muscle tingling		1	1	Minimal
Fainting/dizziness upon standing		1		Minimal
Skin				
Rash	1			Minimal
Red/sunburn skin		1		Minimal
Dry/itchy skin		1		Minimal
Acne		2	1	Minimal
Psychological				
Vivid dreams		1		Mild
Drowsiness	1	2		Minimal
		1	1	Mild
Insomnia			1	Minimal
	1			Mild
Agitation	1	1	1	Minimal
		1		Mild
Irritability	1	1	1	Minimal
		1		Mild
Confusion	1	1		Minimal
Difficulty concentrating		1		Minimal
Aggression	1			Minimal

[a]Number of participants experiencing an adverse event (participant counted only once for each adverse event).

abilities after 28 days of daily citicoline administration (McGlade et al., 2012). Effects of supplementation may also be examined in a sample with greater socioeconomic and ethnic diversity. Finally, considering that abnormal dopaminergic activity may play a role in psychiatric disorders such as ADHD (Andersen, 2003; Volkow & Li, 2004) and substance use disorders (Volkow & Li, 2004), examining citicoline supplementation in a psychiatric population may be warranted.

Few studies have investigated low doses of citicoline in a healthy sample, with some notable exceptions (McGlade et al., 2012). Moreover, this study may be the first to

Table 10. Adverse Events by Body System and Severity, Separated by Dose (Percentage).

Body system and preferred system	500 mg[a]	250 mg[a]	Placebo[a]	Severity
Overall	32	36	32	
Total participants reporting side effects	13	17	12	
Ears/eyes/head				
Headache	2.7	2.7	1.3	Minimal
	1.3	1.3		Mild
Blurred vision		1.3		Mild
Mouth				
Dry mouth	4.0	4.0	2.7	Minimal
	1.3	1.3	1.3	Mild
Slurred speech	2.7	1.3		Minimal
Drooling/pooling		1.3		Minimal
Nose/throat/chest				
Sore throat			4.0	Minimal
Runny nose	1.3		2.7	Minimal
Gastrointestinal				
Decreased appetite		1.3		Minimal
		1.3		Mild
Thirst increase	2.7	4.0	2.7	Minimal
	2.7	2.7		Mild
Diarrhea	1.3	1.3	1.3	Minimal
Abdominal pain			1.3	Minimal
Musculoskeletal/neurological				
Complaints of muscle sprain or aches		1.3		Minimal
Muscle tingling		1.3	1.3	Minimal
Fainting/dizziness upon standing		1.3		Minimal
Skin				
Rash	1.3			Minimal
Red/sunburn skin		1.3		Minimal
Dry/itchy skin		1.3		Minimal
Acne		2.7	1.3	Minimal
Psychological				
Vivid dreams		1.3		Mild
Drowsiness	1.3	2.7		Minimal
		1.3	1.3	Mild
Insomnia			1.3	Minimal
	1.3			Mild
Agitation	1.3	1.3	1.3	Minimal
		1.3		Mild
Irritability	1.3	1.3		Minimal
		1.3		Mild
Confusion	1.3	1.3		Minimal
Difficulty concentrating		1.3		Minimal
Aggression	1.3			Minimal

[a]Percentage of total number of participants who completed both visits of the study (n = 75).

examine citicoline supplementation in a healthy adolescent male population. Our findings indicated that 28 days of daily citicoline supplementation enhances motor and attentional abilities and decreases impulsivity in male adolescents, which is consistent with previous findings of similar improvements within clinical populations. Implications include use of citicoline to treat disorders of attention, as well as to enhance normative attentional functioning in certain groups of adolescents—for example, those at risk for scholastic failure or addiction, as well as those with disorders involving poor attention and impulse control, such as ADHD. Citicoline may also be used to enhance normative

Table 11. Metabolic Parameters by Group at Baseline (V1) and Study Completion (V3) Including Significance of Within-Group Change Between Visits (*p*).

	Placebo (*n* = 51)			Cognizin (*n* = 24)		
Measure	*M*	*SD*	*p*	*M*	*SD*	*p*
Creatinine (mg/dL) V1	0.79	0.03	.001	0.81	0.02	0.03
Creatinine (mg/dL) V3	0.85	0.04		0.83	0.03	
Glucose (mg/dL) V1	89.42	2.33	.852	89.96	1.80	0.16
Glucose (mg/dL) V3	90.04	3.01		93.35	2.02	
Alkaline phosphatase (U/L) V1	181.63	19.20	.190	201.00	14.12	0.69
Alkaline phosphatase (U/L) V3	177.13	18.28		206.51	14.77	
Aspartate Aminotransferase (U/L) V1	22.58	1.09	.557	24.43	0.84	0.15
Aspartate Aminotransferase (U/L) V3	23.63	1.68		23.45	0.76	
Alanine Aminotransferase (U/L) V1	16.58	0.85	.292	19.82	2.15	0.23
Alanine Aminotransferase (U/L) V3	20.04	3.51		17.86	1.46	
γ-glutamyl transferase (U/L) V1	19.67	1.11	.089	18.96	1.16	0.90
γ-glutamyl transferase (U/L) V3	18.25	0.85		18.84	1.04	
Calcium (mg/dL) V1	9.84	0.06	.168	9.80	0.05	0.84
Calcium (mg/dL) V3	9.78	0.73		9.79	0.39	
Protein (g/dL) V1	7.40	0.06	.095	7.35	0.05	0.23
Protein (g/dL) V3	7.28	0.07		7.30	0.05	
Albumin (g/dL) V1	4.45	0.06	.115	4.37	0.04	0.28
Albumin (g/dL) V3	4.38	0.05		4.34	0.04	
Bilirubin (mg/dL) V1	0.70	0.09	.268	0.69	0.05	0.91
Bilirubin (mg/dL) V3	0.77	0.09		0.67	0.06	

functioning in adolescents, particularly those at risk for negative outcomes related to lower selective attention and heightened impulsivity often seen in adolescents and young adults. Considering the positive safety profile of citicoline in adolescent males, this dietary supplement supports a low risk/high reward ratio and shows promise in treating conditions of higher prevalence in this population.

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