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Creatine supplementation does not improve cognitive function in young adults

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ABSTRACT

Creatine supplementation has been reported to improve certain aspects of cognitive and psychomotor function in older individuals and in young subjects following 24 and 36 h of sleep deprivation. However, the effects of creatine supplementation on cognitive processing and psychomotor performance in non-sleep deprived young adults have not been assessed with a comprehensive battery of neurocognitive tests. The primary objective of this study was to examine the effects of creatine supplementation on cognitive processing and psychomotor performance in young adults. Twenty-two subjects (21±2 yr) ingested creatine (0.03 g/kg/day) or placebo for 6 weeks in a double-blind placebo-controlled fashion. Subjects completed a battery of neurocognitive tests pre- and post-supplementation, including: simple reaction time (RT), code substitution (CS), code substitution delayed (CSD), logical reasoning symbolic (LRS), mathematical processing (MP), running memory (RM), and Sternberg memory recall (MR). There were no significant effects of group, no significant effects of time, and no significant group by time interactions for RT, CS, CSD, LRS, MP, RM, and MR (all $p>0.05$), indicating that there were no differences between creatine and placebo supplemented groups at any time. These results suggest that six weeks of creatine supplementation (0.03/g/kg/day) does not improve cognitive processing in non-sleep deprived young adults. Potentially, creatine supplementation only improves cognitive processing and psychomotor performance in individuals who have impaired cognitive processing abilities.

1. Introduction

Phosphocreatine acts as an energy buffer in both skeletal muscle and brain tissue. During physical activity, phosphocreatine donates its phosphate to adenosine diphosphate to produce adenosine triphosphate (ATP), to maintain ATP. Similarly, during brain activity, brain phosphocreatine levels decrease rapidly in order to maintain constant ATP levels [1,2]. Creatine monohydrate, which can increase muscle [3,4] and brain creatine levels [5–7], is an inexpensive and popular dietary supplement among athletes (reviewed in [8]), which can improve muscle and brain performance.

Subsequent to increases in muscle creatine, there are increases in strength and lean body mass and improvements in exercise performance [9,10]. There are several systemic and peripheral changes following creatine supplementation (e.g. metabolic adaptations, changes in protein turnover, hormonal alterations, stabilization of lipid membranes, molecular modifications), which collectively cause these muscular and performance related adaptations (reviewed in [11]). Recent studies have demonstrated central metabolic changes resulting from creatine supplementation, which suggests this nutrient could alter not only muscle, but cognitive function [5–7,12–16].

Creatine supplementation can increase brain creatine (9%) [5–7] and phosphocreatine (4%) [6] in healthy adults, as assessed with nuclear magnetic resonance spectroscopy. The creatine supplementation protocols varied considerably in these studies, including: 20 g/day for 7 days [7], 20 g/day for 28 days [5], and 0.3 g/kg/day for 7 days followed by 0.03 g/kg/day for 7 days [6]. One group reported no increase in brain creatine following ingestion of 20 g/day for 5 days. [17]. As increased muscle creatine following creatine supplementation improves muscular performance, increasing brain creatine levels should improve cognitive processing [12–16]. McMorris et al. [13] demonstrated a significantly smaller decrement in performance on random movement generation, choice reaction time, balance, and mood state tests (following 24 h of sleep deprivation) (creatine $n=10$, placebo $n=9$; age≈21 yr; 20 g creatine/day for 7 days) [13] and improved performance on a random number generation task (following 36 h of sleep deprivation) (creatine $n=10$, placebo $n=10$; age≈21 yr; 20 g creatine/day for 7 days) [12] following creatine ingestion. In elderly subjects (creatine n=15, placebo $n=17$; age≈76 yr), 20 g of creatine per day resulted in improved performance on forward number recall, forward and backward spatial recall, and a long term memory test, but no effect on backward recall or random number generation performance [16]. In subjects tested in an unstressed state,

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Rae et al. [14] reported that creatine supplementation significantly improved working memory and increased intelligence in young vegetarians (n=45; age≈27 yr; 5 g creatine/day for 6 weeks) and Watanabe al. [15] demonstrated reduced mental fatigue and reduced cerebral oxygenated hemoglobin (i.e. increased oxygen utilization) in the brains of young subjects following creatine supplementation (creatine n=12, placebo n=12; age≈24 yr; 8 g creatine/day for 5 days).

The results of studies published by McMorris et al. [12,13,16] provide evidence that creatine supplementation improves cognitive processing in individuals who are cognitively impaired. Results of studies published by Rae et al. [14] and Watanabe et al. [15] suggest a role for creatine supplementation in subjects who are not temporarily cognitively impaired, but these studies used a limited number of cognitive and no psychomotor measures to test their hypotheses. The purpose of this study was to assess cognitive processing pre- to post-creatine supplementation in young adults using a comprehensive battery of tests. We hypothesized that 6 weeks of creatine supplementation would improve cognitive processing in individuals who are not sleep deprived.

2. Methods

2.1. Experimental design

This study was conducted in the Department of Exercise Science and Athletics at Bloomsburg University. On visits 1 and 2, participants completed the cognitive function tests. Participants then ingested either creatine or placebo supplements for 6 weeks. Following the supplementation phase, participants repeated the cognitive function tests. Testing was conducted at the same time of day for all three visits (±1 h), and subjects reported to the laboratory in a post-prandial state.

2.2. Subjects

Twenty-two non-vegetarian subjects (13 males, 9 females) recruited from the Bloomsburg area completed the study. All participants read and signed an informed consent document approved by the Bloomsburg University Institutional Review Board prior to participation in this study. Subjects were instructed to maintain similar habitual physical activity and dietary behaviors for the duration of the study. Individuals who had previously ingested creatine supplements were permitted to participate in this investigation if they had not ingested creatine within the previous 6 weeks. Descriptive characteristics of the subjects are presented in Table 1.

2.3. Supplementation

Participants were randomly placed into either a creatine or placebo group, and supplements were administered in a double-blind, placebo-controlled manner. Subjects ingested 0.03 g of encapsulated creatine (NutraSense Company, Shawnee Mission, KS) or placebo per kilogram of body weight per day for 6 weeks. Similar supplementation protocols have been previously shown to significantly increase muscle creatine levels [4] and to improve brain performance [14]. Participants were instructed to ingest the supplements with food as this enhances body creatine retention [18].

The creatine used in this study was manufactured by Ferro–Pfanstiehl Laboratories (Waukegan, Illinois). Ferro–Pfanstiehl creatine is produced in a Food and Drug Administration (FDA) monitored facility and Ferro–Pfanstiehl is the only creatine manufacturer that maintains a creatine Drug Master File with the FDA. Every lot of creatine is HPLC tested to ensure purity, is Kosher Certified, and each shipment of creatine is accompanied with a Certificate of Analysis which includes information on: loss on drying, appearance, residue ignition, heavy metals, assay, dicyandiamide, creatinine, identity, arsenic, *E. coli*, *Salmonella*, *Staph. aureus*, Yeasts and molds, and colioforms. All were below acceptable limits. Additionally, an external validation study reported that Ferro–Pfanstiehl creatine contains 100% of what is claimed on the label, and HPLC revealed no other peaks besides creatine, which indicates no contaminants [19].

Table 1
Descriptive characteristics of subjects

	Age (yr)	Height (cm)	Body mass (kg)	BMI (kg/m^2)
Creatine group (n=11; 5 F)	21.0±2.1	171.5±9.6	73.8±13.6	24.9±3.0
Placebo group (n=11; 4 F)	20.6±2.2	171.6±6.6	77.0±7.0	26.1±2.3

2.4. Cognitive processing and psychomotor performance tests

Tests were conducted on the Automated Neuropsychological Assessment Metrics (ANAM) system [20,21]. ANAM consists of computerized tests for precise measurement of cognitive processing in a variety of psychological assessment contexts and is specifically designed for repeated-measures testing. The correct responses and the timing of the stimuli during the cognitive processing and psychomotor performance tests were different for each administration. Specific cognitive processing tests included: simple reaction time, code substitution, logical reasoning, mathematical processing, running memory, and memory recall. The outcome variables for the specific tests, with the exception of simple reaction time, were response speed (milliseconds), response speed of correct responses (milliseconds), and throughput (correct responses/minute). All tests were conducted using a Gateway computer with Pentium III processor and a Gateway VX700 17 monitor.

2.5. Specific cognitive and psychomotor tests

2.5.1. Simple reaction time

Participants were instructed to press the mouse button when the visual stimulus (i.e. *) was presented. The rate of presentation was once every 675 to 1200 ms and the visual stimulus appeared twenty times in the same location each time. The mean of the twenty trials was used in the final analysis.

2.5.2. Logical reasoning

The pairs "# &" or "& #" were displayed with a statement that correctly or incorrectly described the order of the symbols. Participants decided if the statement was true or false and pressed a specific mouse button. The rate of stimulus presentation is variable because each trial ends as soon as the subject responds. The interstimulus gap between stimuli was 950 to 1200 ms and 24 presentations were given.

2.5.3. Memory search (Sternberg task)

Subjects were asked to memorize a set of six letters displayed on the monitor for 20 s. Thereafter, "probe" letters were presented one at a time, and subjects pressed a specific mouse button to indicate whether or not the letter was in the memorized set. The rate of stimulus presentation is variable because each trial ends as soon as the subject responds. The interstimulus gap between stimuli was 950 to 1350 ms, there was a 50% hit ratio, and 40 presentations were given.

2.5.4. Running memory

A randomized sequence of numbers was presented one number at a time, and participants pressed a specified mouse button key if the letter on the screen matched/did not match the letter that immediately preceded it. The stimulus was on the screen for 500 ms, and the lapse time was 1000 ms (500 ms to respond after the stimulus disappears). The rate of stimulus presentation is variable because each trial ends as soon as the subject responds. The interstimulus gap between stimuli was 950 to 1200 ms, there was an equal number of same/different responses, and 160 presentations were given.

Table 2
No effect of 6 weeks of creatine or placebo supplementation on cognitive processing

	Creatine		Placebo		G×T *p*-value	*F*
	Pre	Post	Pre	Post		
Simple reaction time	226.2±35.5	231.5±48.1	227.4±43.7	211.7±17.1	0.18	1.91
Code substitution						
Correct	797.3±146.6	773.1±112.1	821.2±155.0	766.6±70.0	0.56	0.35
All	798.6±145.7	780.5±114.1	817.7±152.6	770.4±68.4	0.72	0.13
Throughput	72.5±11.5	75.0±8.5	72.6±12.5	74.1±7.4	0.64	0.23
Code sub. delayed						
Correct	804.8±144.5	807.6±128.7	846.4±221.4	818.4±145.0	0.56	0.43
All	818.2±161.3	825.7±145.9	858.3±235.0	828.8±147.0	0.54	0.39
Throughput	69.1±12.3	68.0±10.7	68.0±15.9	70.4±12.3	0.45	0.59
Logical reason.						
Correct	2106.9±912.7	1871.6±497.9	1797.7±596.6	1620.4±480.5	0.65	0.21
All	2036.9±703.6	1920.9±649.7	1814.9±577.9	1650.2±483.9	0.97	0.00
Throughput	28.9±13.0	32.3±9.9	30.4±9.2	40.4±22.3	0.46	0.58
Math. processing						
Correct	2155.7±477.1	2110.1±483.2	2277.4±402.2	2176.3±382.3	0.67	0.19
All	2167.0±478.8	2095.9±482.8	2277.9±402.8	2198.5±401.6	0.94	0.00
Throughput	25.3±7.6	26.3±7.3	24.1±5.5	24.7±5.4	0.86	0.03
Running memory						
Correct	483.0±108.1	468.3±94.1	445.0±56.8	427.9±52.7	0.96	0.00
All	501.0±139.7	479.7±108.0	448.4±59.5	430.8±57.4	0.71	0.15
Throughput	118.8±35.5	123.9±28.5	125.7±18.0	127.5±16.4	0.58	0.32
Memory recall						
Correct	482.9±108.1	468.2±94.1	445.0±56.8	428.0±52.7	0.68	0.18
All	501.0±140.0	479.7±108.0	448.4±59.5	430.7±57.3	0.62	0.25
Throughput	118.8±35.5	124.0±28.5	126.0±18.0	128.0±16.4	0.52	0.43

Data are presented as response times (ms) for correct responses, response times (ms) for all responses, and as throughput (correct responses/min) (mean±SD). DF=20.
G×T = Group by Time *p*-value.

2.5.5. Code substitution immediate and delayed

A key containing 9 unique symbols paired with 9 unique digits was displayed. A "test" pair (i.e. one symbol and one digit) was presented at the bottom of the screen, and participants pressed a specific mouse button to indicate if the "test" pair matched the associated pair in the key at the top of the screen. In the "immediate" test, the recognition memory trial occurred immediately following the learning phase. The rate of stimulus presentation is variable because each trial ends as soon as the subject responds. The interstimulus gap between stimuli was 750 to 950 ms and 72 presentations were given. During the delayed test, only the "test" stimuli were presented. The rate of stimulus presentation is variable because each trial ends as soon as the subject responds. The interstimulus gap between stimuli was 750 to 950 ms and 36 presentations were given. The delayed test took place approximately 5 min after the immediate test.

2.6. Anthropometry

Body mass was measured to the nearest 0.1 kg on a Health-o-Meter Pro Series scale (Model # 160 LB, Sunbeam Products, Inc., Bridgeview, IL). Height was measured to the nearest 0.5 cm using a wall mounted stadiometer. Body mass index (BMI) was computed using the equation: BMI=weight (kg)/height (m^2).

2.7. Statistical analyses

Sample size was estimated based on data from McMorris et al. [13] and conducted assuming a power $(1-\beta)$ of 0.80 and $\alpha=0.05$. It was estimated that ten subjects in each group would be needed to locate a significant effect. A repeated-measures ANOVA with a grouping factor was used to assess the pattern of change between groups from pre to post-supplementation (group×time interaction term). Significance was set *a priori* at $p\leq0.05$. Test–retest intraclass reliability coefficients for the cognitive processing tests are: simple reaction time $R=0.61$, code substitution $R=0.76$, logical reasoning $R=0.94$, mathematical processing $R=0.92$, running memory $R=0.77$, and memory recall $R=0.77$.

3. Results

There were no significant differences in age ($p=0.70$), height ($p=0.98$), body mass ($p=0.48$), or body mass index ($p=0.30$) between creatine and placebo groups (Table 1). There was no significant effect of group ($p=0.52$), no significant effect of time ($p=0.50$), and no significant group by time interaction for simple reaction time ($p=0.18$), indicating that there was no difference between creatine and placebo supplemented groups at any time (Table 2). Similarly, there were no significant effects of group, no significant effects of time, and no significant group by time interactions for code substitution (immediate and delayed), logical reasoning symbolic, mathematical processing, running memory, and memory recall (all $p>0.05$) (Table 2).

4. Discussion

We hypothesized that creatine supplementation would improve cognitive processing and psychomotor performance in college aged individuals. It has been previously reported that creatine supplementation can increase brain creatine and phosphocreatine [5–7], and that this may subsequently alter cerebral hemoglobin oxygenation [15], cognitive processing, and psychomotor performance [12–16]. The most convincing evidence of an effect of creatine on cognitive processing and psychomotor performance appears to be when subjects are cognitively impaired by 24 to 36 h of sleep deprivation and exercise [12,13] or aging [16]. In the current study we used a comprehensive battery of tests to assess both complex and simple cognitive processing tasks pre- and post-creatine supplementation in non-sleep deprived individuals.

Contrary to the results of previous studies, we were unable to demonstrate any effect of the creatine supplement on cognitive processing or psychomotor performance. Subjects in the current study

experienced no improvement in simple reaction time (RT), code substitution (CS), code substitution delayed (CSD), logical reasoning symbolic (LRS), mathematical processing (MP), running memory (RM), and Sternberg memory recall (MR) following 6 weeks of creatine ingestion. Differences in methodology could explain our apparently discrepant findings with the studies of creatine supplementation and sleep deprivation. Based on the data of McMorris et al. [12,13,16], it is possible that creatine only has a measureable effect on cognitive processing and psychomotor performance in individuals who are either permanently (i.e. disease, aging) or temporarily (i.e. sleep deprivation and exercise) cognitively impaired. Specifically, creatine may be able to blunt the decrease in cognitive processing or psychomotor performance during sleep deprivation, but may not improve cognitive processing or psychomotor performance in well rested/unstressed individuals.

It is difficult to explain why our results differ from those of Watanabe et al. [15] and Rae et al. [14] who also tested their subjects in an unstressed and rested state. Potentially, the tasks used by Watanabe et al. [15] and Rae et al. [14] were more cognitively challenging than those used in the current study, placed a greater demand on cerebral ATP re-synthesis, and thus produced a measurable effect from the creatine. This, however, seems unlikely, in that the tasks used in the current study included complex central executive tasks, which may require more energy, as well as simpler tasks. Rae et al. [14] examined the effects of creatine supplementation on brain performance of vegetarians who are known to have lower plasma [22], red blood cell [23], and muscle creatine [24]. Because those with the lowest muscle creatine have the largest increase in muscle and blood creatine following creatine ingestion, it is possible that the vegetarian subjects in the study by Rae at al. [14] experienced a larger increase in brain creatine than subjects in the current study, who were not vegetarians. Recently Pan and Takahashi [7] demonstrated that subjects with the lowest initial brain PCr/ATP ratio, as may be the case with vegetarians, had the greatest increase in brain PCr/ATP following 7 days of creatine ingestion. This may explain the differences between our findings and those of Rae et al. [14].

The supplementation protocol used in the current study (0.03 g/kg/day for 6 weeks; ≈2.2 g/day) differs from the protocols used by Rae et al. (5 g/day for 6 weeks) [14] and Watanabe et al. [15] (8 g/day for 5 days), and may be a factor in our negative findings. Our supplementation protocol was based on the seminal paper by Hultman et al. [4] in which it was demonstrated that the ingestion of 20 g of creatine/day for 6 days, 20 g of creatine for 6 days followed by 2 g/day for 28 days, and 3 g of creatine (0.03 g/kg of body weight) for 28 days all cause similar increases in muscle total creatine. Importantly, the majority of supplemental creatine was unabsorbed in both the high dose loading (17% creatine retained following 20 g of creatine/day for 6 days) and low dose longer term supplementation protocols (30% absorbed during the first 14 d and 12% during the final 14 d following 0.03 g of creatine/kg for 28 d) [4]. Given that the increase in muscle creatine is directly correlated with the improvement in post-supplementation performance, we believe that our supplementation protocol provided an adequate amount of creatine. Also, considering the smaller mass of the brain relative to total body skeletal muscle mass, we are confident that we provided sufficient creatine to our subjects.

Whether our supplementation protocol was adequate to increase brain creatine cannot be resolved from the current study or from other studies where cognitive processing is the primary outcome without assessment of changes in brain creatine and phosphocreatine [12–16]. Tissue creatine uptake is both a function of dose and duration of ingestion, much like many other nutrients. It could be viewed that we provided less creatine than Rae et al. [14] (300 vs. 97 g), less than McMorris et al. [12,13,16] (140 vs. 97 g) but more than Watanabe et al. [15] (40 vs. 97 g). We are unaware of any human research that provides real time data on creatine ingestion and brain creatine accumulation, and additionally, we are unaware of human studies that provide data indicating that doses of creatine necessary to increase tissue concentrations are different for muscle and brain tissue. It is known that the majority of creatine ingested, even at a rate of 0.03 g/kg/day is excreted. In two recent studies that used similar creatine supplementation protocols (20 g/day for 5 days vs. 20 g/day for 7 days), brain creatine increased 5% in one study [7], but did not increase in the other study [17]. This indicates that supplementation dose and duration are not the only factors influencing brain creatine accumulation [7,17].

The greatest known determinant of brain creatine accumulation following creatine supplementation is basal brain creatine [7]. Muscle and brain both have very high basal tissue content, and tissue creatine uptake is inversely related to basal levels ($r \approx -0.74$) [7,25]. It appears that the potential to increase brain creatine is smaller than the potential to increase muscle creatine (≈9% vs. ≈15 to 30%) [3–7,25]. This may indicate that basal brain creatine is greater than basal muscle creatine and/or the upper limit of brain creatine is lower than the upper limit of skeletal muscle creatine content.

In any study of creatine supplementation there is the possibility that some subjects did not respond (i.e. <10% increase in muscle creatine) to the supplementation because of higher than normal basal muscle creatine levels. It has been demonstrated that muscle creatine uptake can be enhanced in the presence of insulin [26] or a meal capable of producing hyperinsulinemia [18,27–29]. Although subjects in the current study were instructed to ingest their supplement with a meal, which may enhance muscle creatine uptake, few data are available to support how this may alter brain creatine uptake. Recently, Pan and Takahashi [7] reported that the increase in brain creatine in response to creatine supplementation differs by region of the brain and is based on initial brain creatine levels. Moreover, memory training increases brain creatine in some, but not all areas of the brain [30]. It is unknown if subjects in the experimental group of the current study significantly increased brain creatine, and if so, if creatine was increased in the areas of the brain most related to the cognitive processing tasks assessed (e.g. working memory central executive tasks and prefrontal cortex and hippocampus).

We based our sample size on the effect size demonstrated by McMorris et al. [13] who reported differences in random movement generation, choice reaction time, balance, and mood state in creatine ($n=10$) and placebo ($n=9$) supplemented subjects. Similar sample sizes have been used to show improved performance on a random number generation task (creatine $n=10$, placebo $n=10$) [12], and reduced mental fatigue and reduced cerebral oxygenated hemoglobin (creatine $n=12$, placebo $n=12$) [15]. A post-hoc power analysis based on our data demonstrates that an increase in sample size to the number of subjects tested by Rae et al. ($n=45$ crossover study) [14] would not approach the number of subjects needed to detect a difference between the two groups in the current study.

In summary, we report that 6 weeks of creatine supplementation (0.03 g/kg/day) does not improve cognitive processing or psychomotor performance in rested young males and females. The dose used in this study would be comparable to an individual taking ≈2.2 grams of creatine per day. Creatine may only be effective in improving cognitive processing in individuals who have initially low basal levels of brain creatine and/or individuals who are either permanently (i.e. disease, aging) or suffering from only temporary (i.e. sleep deprivation plus exercise) cognitive impairments. Future research should attempt to assess the relationships between changes in brain creatine, cognitive processing, and psychomotor performance following creatine supplementation.

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opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or as reflecting the views of the Army or the Department of Defense. Human subjects participated in these studies after giving their free and informed voluntary consent. The investigators have adhered to the policies for protection of human subjects as prescribed in Army Regulation 70-25, and the research was conducted in adherence with the provisions of 32 CFR Part 219. Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

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