Cognitive effects of creatine ethyl ester supplementation

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Supplementation with creatine-based substances as a means of enhancing athletic performance has become widespread. Until recently, however, the effects of creatine supplementation on cognitive performance has been given little attention. This study used a new form of creatine – creatine ethyl ester – to investigate whether supplementation would improve performance in five cognitive tasks, using a double-blind, placebo-controlled study. Creatine dosing led to an improvement over the placebo condition on several measures. Although creatine seems to facilitate cognition on some tasks, these results require replication using objective measures of compliance. The improvement is discussed in the context of research examining the influence of brain energy capacity on cognitive performance. ***Behavioural***

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Introduction

This study investigates the cognitive effects of creatine, a naturally occurring amino acid and a popular nutritional supplement. Creatine has been widely used to improve muscle performance during exercise, especially those who require good anaerobic performance (Volek and Rawson, 2004). Methods of ingestion include capsules, serum liquid, caplets and most commonly a powder mixed into water or fruit juice. Upon supplementation, creatine has been shown to significantly increase energy supply to muscle cells (Burke *et al.*, 2003) and to neurons (Klivenyi *et al.*, 1999; Rae *et al.*, 2003). However, little attention has been paid to the effects of this substance on mental performance, with only a single published study on this topic (Rae *et al.*, 2003).

Creatine has been extensively investigated for its possible role as a therapeutic treatment and has reported success for neuromuscular diseases, such as muscular atrophy (Klivenyi *et al.*, 1999), McArdle's disease (Vorgerd *et al.*, 2000), Parkinson's disease (Wyss and Schulze, 2002), metabolic problems (Stockler *et al.*, 1994, 1996) and ultimately as a neuroprotective agent (Item *et al.*, 2001; Rae *et al.*, 2003). Klivenyi *et al.* (1999) investigated mice suffering with the neurodegenerative disease amyotrophic lateral sclerosis and found that the life span of the mice was extended two-fold when given creatine supplements compared to those given conventional drug treatments. Klivenyi *et al.* (1999) suggested that increased energy availability to injured nerve cells prolonged their life span.

Further study has shown that significant increases in anaerobic strength occur in patients with chronic neuromuscular disorders when given creatine supplements against a control group given a placebo (Burke *et al.*, 2003). In addition, researchers investigating the causes of energy deficits present in fibromyalgia/chronic fatigue syndrome found that stored creatine was severely depleted, and that fatigue was alleviated by creatine supplementation (Amital *et al.*, 2006).

Muscle and neural cells carry out a range of processes that require energy. When a cell demands energy, dephosphorylation occurs with the aid of the enzyme ATPase that breaks down adenosine triphosphate (ATP) to release energy. In conditions such as strenuous physical exercise or demanding mental tasks, such as intelligence tests, dephosphorylation of ATP can only fuel cells to a limited extent. Creatine can act as a 'secondary' substance that can form phosphate bonds of higher energy content than of ATP. Creatine is a significantly smaller molecule than ATP; hence, creatine is able to travel the distance to energy-demanding processes much faster and more efficiently than ATP (Schlattner *et al.*, 2006). Creatine stores are limited; although it is synthesized in the body, it must still be obtained through appropriate diet.

Several studies have found evidence showing the importance of creatine in neurons and subsequent cognitive ability. Faulty DNA can lead to severe disruptions in the normal functioning of cell energy cycles and can often result in neurological defects, including cognitive impairment and mental retardation (Item *et al.*, 2001). For example, Stockler *et al.* (1994) found supplementation with creatine monohydrate reversed the severe abnormalities, including developmental delays,

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caused by a complete absence of creatine in the brain of an infant following a genetic mutation. Further analysis indicates that cognitive improvement is correlated with the level of brain creatine (Stockler *et al.*, 1994, 1996; Item *et al.*, 2001).

Although little research has examined the influence of creatine on cognitive performance, Jost *et al.* (2002) found that deletion of cytosolic brain-type creatine kinase in mice resulted in slower learning of a spatial task by diminishing habituation. This suggests that creatine is strongly implicated in brain plasticity as well as metabolism. The amount of creatine available in the brain is controlled by the rate of synthesis as well as the transport of creatine into cortical neurones; deficits in either the creatine transporter or in the enzymes that synthesize creatine can result in neurological deficits (Stockler *et al.*, 1996).

Creatine is thus important for brain-energy homoeostasis and a disruption in this system can lead to clinical symptoms. What remains unclear is whether creatine can play a role in increasing performance on cognitive tasks that require high neural energy use. Only one study has examined this issue. Rae *et al.* (2003) investigated whether creatine monohydrate supplementation for a 6-week period would enhance cognitive performance in 45 young adults who were all vegetarians. Participants performed an intelligence test (Raven's Advanced Progressive Matrices) and a working memory test (Backward Digit Span). Rae *et al.* (2003) used a double-blind procedure, with a placebo group who were given maltodextrin, a safe complex carbohydrate derived from starch. They found that creatine monohydrate supplementation had a significant positive effect on both the tasks, and showed that the speed of processing demanded in such tests was increased after supplementation. These results indicate that creatine monohydrate supplementation may play a role in increasing the capacity of brain energy stores, which in turn seem to improve cognitive performance. However, the fact that all participants were vegetarian in this study presents the possibility that they may have been low in creatine at the start of the study, with improvements in performance due to raising creatine to optimal levels over the course of the study.

Various forms of creatine exist, but the two most commonly available are creatine monohydrate, which is creatine with an additional water molecule attached (used in all the studies reported above), and creatine ethyl ester (CEE), which is creatine monohydrate with an extra ester bond attached to its molecular structure. Currently, no studies have investigated the role and potency of CEE when compared with conventional creatine monohydrate.

There are several reasons why CEE use may be more favourable than the monohydrated version. Creatine monohydrate has been reported to cause bloating and water retention (Fuld *et al.*, 2005), as it requires a loading period of up to 2 weeks, involving five to six daily doses of 10 mg, to raise cellular creatine levels, at which point dosing is reduced to one serving per day (Volek and Rawson, 2004). This extended loading phase is related to the low absorption efficiency rate (10%) of creatine monohydrate (Persky *et al.*, 2003b). Creatine monohydrate is known to be hydrophilic, as it attracts additional water to move against the concentration gradients where it accumulates inside intracellular fluid (Persky *et al.*, 2003a); a long loading period ensures adequate absorption in the muscle cells. Creatine ethyl ester may have advantages over the monohydrated form in that its absorption efficiency rate in the body is almost maximal (99%; Gardiner and Heuer, 2006), which diminishes the need for a loading stage and also requires a much lower dosage per day, around 2–5 mg. Athletes supplementing with CEE anecdotally report no water bloating/retention and further report significant muscle strength/muscle size gains that seem to be as effective as that of taking 10 mg of creatine monohydrate.

No scientific literature exists on CEE, either examining athletic performance or cognitive effects. This study aimed to examine the cognitive effects of supplementing with this form of creatine, using a double-blind, placebo-controlled design. A battery of tests was used to examine a wide range of cognitive abilities, which involved a test of general intelligence, and a series of four simple cognitive tasks measuring spatial ability, memory recall, response inhibition and reaction time.

Methods

Participants

There were 34 participants (including 12 females) who completed the study, with a mean age of 21 years (SD: 1.38; range: 18–24). Participants were excluded, if they presented with a medical history of drug and/or alcohol abuse, diagnosed psychiatric disorders, diabetes, renal insufficiency (kidney dysfunction) or had recently or were currently supplementing with a creatine-based substance. None of the participants was vegetarian. The study was approved by the local ethics committee and all participants signed a consent form after having read an information sheet detailing the research. Three participants from each group did not complete the study and therefore their data were excluded from the analysis.

Design

This study had a two-factor mixed-measures design. The unrelated variable was experimental group, with two levels – creatine and placebo. The related measure was time – participants were measured twice on all tasks, once before commencing consumption of the supplements and once after having consumed the supplements for 2 weeks. To minimize the effects of experimenter and

participant expectancies, neither the participants nor the experimenter knew the condition to which participants had been allocated.

Apparatus

Participants completed a battery of five PC-based cognitive tests, based on widely used and validated paradigms. The tests consisted of Memory Scanning, Number-Pair Matching, Sustained Attention and Arrow Flankers, followed by an IQ test. For the first four tests (obtained from *penscreen.com*) participants were instructed to use the left and right arrows on the keyboard to respond to information presented on screen. For all tasks, data were collected by the computer automatically. Order of presentation of the first four tasks was randomized; the IQ test was always presented last.

The Memory Scanning task (Sternberg, 1975) involved the presentation of five numbers on the screen, which participants were required to memorize. After memorizing the numbers, the screen changed to show new digits one at a time. Participants had to press the left arrow key, if the digit presented was in the initial set of memorized digits, or the right arrow key, if it was not. There were six measures of memory scanning performance: mean reaction time for correct responses, stimulus number in set number of incorrect responses, stimulus number in set mean reaction time for correct responses, stimulus number not in set number of incorrect responses, stimulus number not in set, overall mean correct reaction time and total number of errors. There were 76 trials that took approximately 4 min to present. Upon completion of the task, the screen automatically switched to the next task.

The Number-Pair Matching task was based on the flanker paradigm described by Eriksen and Eriksen (1974). Sets of five digits appeared on the computer screen one set at a time. Participants inspected the second and fourth digits of the set and pressed the left arrow key, if the numbers were the same, or the right arrow key, if they were different. In some trials, the remaining digits (distracters) were all different from the target digits (neutral distracters); in other trials some of the distracters were the same as target digits (active distracters). There were 10 performance measures: matched pairs with neutral distracters (reaction time and number incorrect), matched pairs with active distracters where the targets were the same as the distracters (reaction time and number incorrect), nonmatched pairs with neutral distracters (reaction time and number incorrect) and nonmatched pairs with same distracters (reaction time and number incorrect). Overall reaction time and total number incorrect were also calculated across the groups. There were 28 trials, which took approximately 3 min to present. Preliminary analysis indicated there were no systematic differences between distractor types or pair type; therefore, only the aggregated measures of performance (overall reaction time and total number incorrect) are reported in the results.

The Sustained Attention task (Dockree *et al.*, 2005) involved the presentation of numbers on screen one at a time. Participants responded by pressing the left arrow key to every number unless it was a 3, where they should not respond. There were 36 trials, which took approximately 3 min to present. Upon completion, the screen automatically switched to the next task.

In the Arrow Flanker task (Eriksen and Eriksen, 1974), participants were presented with five symbols on screen. The middle one was always an arrow and if that middle arrow pointed to the left, the correct response was to press the left arrow key. If the middle arrow pointed to the right, the correct response was to press the right arrow key. If the middle symbol was not an arrow, participants were instructed to make no response and wait for the next trial. There were nine performance measures: reaction time and number incorrect for congruent trials (arrows in the same direction as the target), neutral trials (flankers were squares rather than arrows) and incongruent trials (arrows in the opposite direction to the target). Overall reaction time, number incorrect and number of false alarms (in response to no-go stimuli) were also calculated. There were 38 trials, which took approximately 3 min to present. Upon completion, an Internet browser window opened for the final task. Preliminary analysis indicated there were no systematic differences between congruent, neutral or incongruent trials; therefore, only the three, aggregated, measures are reported in the results.

The final task participants undertook was a modified version of Raven's Advanced Progressive Matrices (e.g. Raven *et al.*, 1998) presented on a PC using Macromedia Flash Player (*http://iqtest.dk/main.swf*). The difficulty of the 39 questions gradually increased and was constrained by a 40-min time limit.

Procedure

Participants were tested on two separate occasions over a 2-week period, once at the beginning of the study and once at the end, with testing taking place at the same time on each occasion. Participants were seated in front of a PC to perform the cognitive tasks. The tasks were automated so that one task followed the next and instructions were presented on screen. Testing took approximately 50 min. At the end of the first testing phase, participants were given a large envelope that contained 15 plastic vials of either 5 g doses of CEE (obtained through the online store Discount Supplements) or a placebo, maltodextrin (obtained from the manufacturer Chemical Nutrition; *http://www.cnpprofessional.co.uk*). Maltodextrin has been used earlier as a placebo in creatine research, and looks and tastes similar to CEE when mixed

with water. Participants were also provided with verbal and written instructions on how to consume the supplements over the course of the next 15 days and were advised to consume on an empty stomach so as to ensure maximum solubility and absorption. Although findings have been inconsistent, with some researchers observing no interaction between creatine and caffeine and others observing a negative interaction (for a review, see Graham and Moisey, 2006), we advised participants to avoid caffeinated substances within 8 h of supplementing. With this exception, participants were instructed to keep to the same routine as normal (e.g. smokers were told to smoke as normal). Participants' scores were collated at the end of each of their two sessions. Although participants were asked to return any unused materials after the final session as a measure of compliance, they were not asked directly whether they had fully complied with the dosing regime. No participant from either group returned any materials. Participants were not asked to guess which condition they had been placed into as a measure of the strength of the blind. At the conclusion of the final session, participants were thanked and fully debriefed.

Results

Preliminary analysis indicated that the baseline performance of both groups of participants was essentially the same with only two significant differences observed. These data are reported in Table 1. There were no sex differences in performance. Different reported degrees of freedom are because of missing data.

Memory Scanning

As expected, there was a significant effect of practice on performance in the Memory Scanning task, with participants performing better at the second time of testing ($P < 0.01$ on all measures). Overall, the main effect of experimental condition did not influence performance on any of the measures (all $P > 0.05$). However, there were significant interactions between time of testing and experimental condition for almost all outcome measures: mean reaction time for correct responses when the stimulus number was in the set [$F(1,32) = 11.90$, $P < 0.01$]; mean reaction time for correct responses when the stimulus number was not in the set [$F(1,32) = 11.92$, $P < 0.05$]; overall mean reaction time [$F(1,32) = 17.39$, $P < 0.01$] and overall number of incorrect responses [$F(1,32) = 8.73$, $P < 0.01$]. The interaction for number correct when the target was absent from the set approached significance [$F(1,32) = 0.18$, $P = 0.084$]. For all the interactions, creatine significantly improved performance [Tukey's HSD (Honestly Significantly Different), $P < 0.01$ for all measures that reached significance; Table 2]. There were no significant interactions for the number of incorrect responses, regardless of whether the stimulus number was in the set.

Number-Pair Matching

There was no significant main effect of experimental (supplementation) condition on either overall reaction time [$F(1,26) = 0.17$, NS] or overall number incorrect [$F(1,26) = 0.39$, NS]. Practice improved performance on overall reaction time [$F(1,26) = 52.35$, $P < 0.01$] and overall number incorrect [$F(1,26) = 9.21$, $P < 0.01$] with performance at the second testing phase significantly better than at the first for both measures (Table 3).

There was a significant interaction between testing phase and experimental condition for overall reaction time [$F(1,26) = 52.67$, $P < 0.01$] with the creatine group responding significantly faster at the second testing phase than the placebo group (Tukey HSD, $P < 0.01$). There was also a significant interaction between testing phase

Table 1 Comparison of performance of creatine and placebo groups before supplementation

Measure	Dependent variable	Mean square value	*F* value	Significant value
Memory Scanning	Stimulus number in set – RT	1545.143	0.026	0.873
	Stimulus number in set – NI	1.286	1.026	0.320
	Stimulus number not in set – RT	51 514.321	0.626	0.436
	Stimulus number not in set – NI	4.321	0.500	0.486
	Overall mean – RT	15 322.321	0.225	0.639
	Overall NI	10.321	0.797	0.380
Number-Pair Matching	Overall RT	11 849.143	0.309	0.583
	Overall NI	1.750	0.116	0.736
Sustained Attention	Number of correct responses	0.036	0.035	0.853
	RT correct responses	54 914.286	5.268	0.030*
	Number of false positives	1.286	3.296	0.081
	Number of correct omissions	2.286	2.249	0.146
	Number of incorrect omissions	5.143	1.724	0.201
Arrow Flankers	Overall number of false alarms	7.000	4.150	0.052
	Overall RT	1955.571	0.176	0.678
	Overall NI	4.321	1.547	0.225
IQ	IQ score	650.893	9.487	0.005**

NI, number of incorrect responses; RT, reaction time (ms).
*Performance of creatine group better at baseline than placebo, $P<0.05$.
**Performance of creatine group worse at baseline than placebo, $P<0.01$.

Table 2 Performance on Memory Scanning measures, by experimental condition

	Stimulus number in set – reaction time		Stimulus number in set – incorrect responses		Stimulus number not in set – reaction time		Stimulus number not in set – incorrect responses		Overall mean reaction time		Overall number incorrect responses	
Week	0	2	0	2	0	2	0	2	0	2	0	2
Creatine	942 (261)	767 (249)**	1.82 (1.81)	0.294 (0.59)**	1142 (302)	891 (309)**	2.47 (3.41)	0.24 (0.56)*	1042 (266)	826 (274)**	4.29 (4.38)	0.65 (1.50)**
Placebo	945 (235)	895 (225)	1.00 (1.71)	1.12 (1.11)	1038 (260)	984 (263)	1.82 (2.59)	1.29 (1.21)	982 (251)	942 (251)	2.82 (3.45)	2.41 (2.27)

Standard deviations are within parentheses.
Significant effects after supplementation: *$P<0.05$; **$P<0.01$.

Table 3 Performance on Number-Pair Matching and Arrow Flankers tasks, by experimental condition

	Number-Pair Matching				Arrow Flankers					
	Mean reaction time (ms)		Number incorrect		Overall false alarms		Mean reaction time (ms)		Number incorrect	
Week	0	2	0	2	0	2	0	2	0	2
Creatine	897 (178)	755 (169)**	4.47 (5.58)	1.88 (3.48)**	1.71 (1.61)	0.88 (1.21)*	555 (99)	492 (95)**	0.5 (0.73)	1.25 (0.34)*
Placebo	856 (211)	857 (214)	4.59 (4.80)	4.53 (4.98)	1.00 (0.79)	1.00 (1.15)	581 (97)	570 (102)*	1.24 (2.04)	1.06 (1.68)

Standard deviations are within parentheses.
Significant effects after supplementation: *$P<0.05$; **$P<0.01$.

and condition for overall number of items incorrect [$F(1,32) = 8.41$, $P < 0.01$] with participants in the creatine group making significantly fewer errors at the second testing phase than the placebo group (Tukey HSD, $P < 0.01$).

Arrow Flankers

There were no significant main effects of treatment condition for any of the measures (all $P > 0.05$). In addition, there were no significant main effects or interactions for either neutral (number incorrect) or incongruent (number incorrect).

There was a significant effect of testing phase for seven of the nine measures; for all of these significant main effects, the second phase was, as expected, associated with better performance than the first phase. There was a significant effect of testing phase on reaction time for congruent stimuli [$F(1,32) = 15.69$, $P < 0.01$]; number of incorrect responses to congruent stimuli [$F(1,32) = 4.14$, $P < 0.05$]; reaction time for neutral flankers [$F(1,32) = 12.81$, $P < 0.01$] and reaction time for incongruent flankers [$F(1,32) = 34.70$, $P < 0.01$]. There were also significant main effects of testing phase for false alarms [$F(1,32) = 4.80$, $P < 0.05$], overall reaction time [$F(1,32) = 19.63$, $P < 0.01$] and overall number incorrect [$F(1,32) = 5.46$, $P < 0.05$].

There was a significant interaction between testing phase and treatment condition for congruent flankers [$F(1,32) = 8.23$, $P < 0.01$] with participants in the creatine condition having shorter reaction times in the second testing phase than those in the placebo group (Tukey HSD, $P < 0.01$; Table 3). There was also a significant interaction between testing phase and treatment condition for reaction times for incongruent flankers [$F(1,32) = 11.87$, $P < 0.01$] and for overall reaction time [$F(1,32) = 9.57$, $P < 0.01$] with performance of the creatine group faster in the second phase than the placebo for both measures (Tukey HSD, $P < 0.01$). Finally, there was a significant interaction between testing phase and treatment condition for false alarms [$F(1,32) = 4.80$, $P < 0.05$] with participants in the creatine condition making fewer false alarms in the second testing phase than those in the placebo group (Tukey HSD, $P < 0.05$).

Sustained Attention

Five outcome measures were used to examine sustained attention: number of correct responses, reaction time for correct responses, number of false positives, number of correct omissions and number of incorrect omissions. There were no significant main effects of experimental condition for number of correct responses, correct omissions or incorrect omissions. There was a significant effect of condition on reaction time [$F(1,30) = 8.306$, $P < 0.01$] with the creatine group having significantly shorter response times. There was also a significant effect of condition on false positives [$F(1,30) = 11.236$, $P < 0.01$] with the placebo group making more false positives.

There were significant main effects of test phase on number correct [$F(1,30) = 4.62$, $P < 0.05$], correct omissions [$F(1,30) = 5.69$, $P < 0.05$] and on reaction time [$F(1,30) = 24.94$, $P < 0.01$]. In all cases participants made significantly fewer errors at the second phase. There were no significant main effects of test phase on either false positives or incorrect omissions.

Table 4 Performance on Sustained Attention tasks, by experimental condition

	Number correct		Mean reaction time (ms)		False positives		Correct omissions		Incorrect omissions	
Week	0	2	0	2	0	2	0	2	0	2
Creatine	31.94 (0.77)	32.25 (0.45)	406 (87)	348 (78)**	0.56 (0.73)	0.25 (0.45)	3.19 (0.98)	2.44 (1.15)**	0.31 (0.70)	0.06 (0.25)
Placebo	31.81 (1.11)	32.06 (0.85)	483 (111)	465 (110)**	1.00 (0.52)	1.06 (0.68)	2.63 (1.03)	2.69 (0.95)	1.13 (2.19)	0.25 (0.45)

Standard deviations are within parentheses.
Significant effects after supplementation: *$P<0.05$; **$P<0.01$.

There was a significant interaction between testing phase and experimental condition for reaction time [$F(1,30) = 6.562$, $P < 0.01$]. Post-hoc tests indicated that there was a significant difference in performance between creatine and the placebo at the second testing phase, with the creatine group having a shorter reaction time in the second testing phase (Tukey HSD, $P < 0.01$; Table 4). There was also a significant interaction between testing phase and experimental condition for correct omissions [$F(1,30) = 7.947$ $P < 0.01$] with the creatine group having fewer correct omissions at the second test phase (Tukey HSD, $P < 0.01$). There were no significant interactions for number correct, number of false positives or number of incorrect omissions for the Sustained Attention task.

IQ

There was a significant effect of test phase on performance in the IQ test [$F(1,32) = 88.98$, $P < 0.01$] with participants scoring a mean of 112 (SD: 9.44) at baseline, and 118 (7.89) at the end of the study. There was no significant main effect of supplement condition [$F(1,32) = 0.56$, NS]. However, the interaction was significant [$F(1,32) = 81.18$, $P < 0.01$]. Pairwise comparisons indicated that participants in the creatine condition performed worse than the placebo group in the first phase of testing, with baseline means for creatine group of 108 (SD: 7.42) and for placebo, 116 (SD: 9.60) (Tukey HSD, $P < 0.01$). Performance of the creatine group also improved significantly over the supplementation period, with the mean of 108 at baseline increasing to 120 (SD: 5.95) at the end of study (Tukey HSD, $P < 0.01$). Further pairwise comparisons indicated that there was no significant improvement in the performance of the placebo group over the supplementation period ($P > 0.05$).

Discussion

The results across the five cognitive tasks were generally consistent. CEE seemed to improve performance in several domains, from tasks that had a strong memory component to tests of attention. Improvements were found consistently for reaction time across measures as well as for some measures of accuracy. This indicates that creatine supplementation seems to improve basic cognitive functions in particular.

This improvement in performance was similar to the increases reported by Rae *et al.* (2003) in their study using creatine monohydrate. In this study, in three of five tasks – Memory Scanning, Arrow Flankers and Raven's Matrices – CEE supplementation significantly improved reaction time performance when compared with the placebo group. The measure of general intelligence used in this study involves global cognitive functioning, including mental rotation skills, decisiveness in stimulus elimination, critical thinking, working memory and logical deduction. Performance in this task also increased in the creatine group when compared with the placebo group, although part of this increase was because of a lower baseline score in the creatine group.

The Number-Pair Matching and Sustained Attention tasks showed more modest improvements than other measures, perhaps because they required less cognitive processing. For example, the Ravens Matrices require the coordination of a range of cognitive abilities to solve each matrix. Generally, creatine acts as a 'backup energy store' second to the ATP cycles that all cells use. In tasks that require less demanding cognitive processing, neurons may rely only on ATP energy cycles, whereas when a highly demanding task is initiated, activation will be more widespread leading to greater demand for energy. It is in such conditions that creatine supplementation could perhaps aid cognitive ability the most, that is, when performing highly complex cognitive tasks that draw upon global cognitive functioning. This is a conjecture that requires further examination.

This study has shown that CEE may be as effective as creatine monohydrate in improving cognitive performance, although this requires explicit testing and a replication of this study, with the addition of a creatine monohydrate group. Some caution with interpretation is therefore warranted, as particularly for the IQ data, the creatinine group was lower at baseline and thus had more scope for improvement. This does not minimize the result – the fact is that this group did respond with improvement over the course of the study on many measures – but this is a limitation of our study as improvements from a higher baseline may be harder to achieve. Participants in both conditions were asked to keep a written diary of how alert they felt. Neither group reported side effects of the supplements, and those in the creatine group gave anecdotal reports of improved cognitive function and reduced experiences of fatigue. Such subjective evidence requires further investigation.

However, such reports, in addition to the quantitative results, support earlier research that has found positive correlations between brain creatine levels and recognition memory (Ferrier *et al.*, 2001) and that creatine supplementation can reduce mental fatigue (Watanabe *et al.*, 2002).

In conclusion, the data show that cognitive ability seems to be improved by CEE supplementation. Although we believe these results are robust, they require replication, preferably using blood glucose testing as an objective measure of compliance. Should these results be replicated, an important next step would be to examine the impact of creatine supplementation over a longer dosing period at the same time as using food diaries, to exclude the possibility that creatine supplementation might merely have been redressing nutritional imbalances.

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