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Creatine Supplementation and Cognitive Performance in Elderly Individuals

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ABSTRACT

The purpose of this study was to examine the effect of creatine supplementation on the cognitive performance of elderly people. Participants were divided into two groups, which were tested on random number generation, forward and backward number and spatial recall, and long-term memory tasks to establish a baseline level. Group 1 (n = 15) were given 5 g four times a day of placebo for 1 week, followed by the same dosage of creatine for the second week. Group 2 (n = 17) were given placebo both weeks. Participants were retested at the end of each week. Results showed a significant effect of creatine supplementation on all tasks except backward number recall. It was concluded that creatine supplementation aids cognition in the elderly.

The purpose of this study was to examine the effect of creatine monohydrate supplementation on the cognitive performance of elderly people. In particular, we were interested in the effect on memory. Both working memory and long-term memory have been shown to deteriorate with age (Parkin & Java, 1999). Long-term memory requires the individual to not only hold information over a period of time but also to recall it. The ability to recall information held in long-term memory is also important in working memory. The idea of working memory was first put forward by Baddeley (1986). Baddeley claimed that working memory involves the person holding information in short-term memory, recalling information from long-term memory, and using both sets of information to make

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decisions and solve problems. Baddeley divided working memory into the central executive, phonological loop, and visuospatial sketchpad. The phonological loop is responsible for the encoding of acoustic and verbal information. The visuospatial sketchpad has the same role as the phonological loop except that it processes visual and visuospatial information. The role of the central executive is to integrate the information in order to make decisions and solve problems.

Functional neuroimaging research has shown that phonological loop tasks depend on the activation of Broca's area and the left-hemisphere premotor cortex, while visuospatial tasks activate the right-hemisphere premotor cortex (Smith & Jonides, 1999). Research using positron emission tomography (Deiber et al., 1991; Frith et al., 1991) has shown that central executive tasks recruit large areas of the prefrontal cortex. Moreover, other parts of the brain are also active (Critchley et al., 2003), as storage of memory is thought to be distributed throughout the neocortex (see Gazzaniga et al., 2002, for a discussion on this point). Thus, the neocortex is important in both working memory and long-term memory. Also of importance in memory is the hippocampus, which is the region responsible for the consolidation of memory. Consolidation requires energy (Schachter et al., 1996) as does the whole of the memory process, in particular recall of information by the dorsolateral prefrontal cortex from the neocortex (Nyberg et al., 1996).

The energy for cognitive performance depends on the hydrolysis of adenosinetriphosphate (ATP) to adenosinediphosphate and inorganic phosphate. The resynthesis of ATP by creatine kinase is dependent upon phosphorylcreatine and the process results in the degradation of phosphorylcreatine, which requires the presence of creatine for replenishment. Deficiency in creatine is a major limitation in this process. However, magnetic resonance spectroscopy studies have shown that creatine monohydrate supplementation results in significant increases in creatine concentrations in the human brain (Dechent et al., 1999; Lyoo et al., 2003). Furthermore, recent research has found that creatine supplementation can have a beneficial effect on cognitive performance in young adults (Watanabe et al., 2002; Rae et al., 2003; McMorris et al., 2006a). Given that recall from memory deteriorates with age, and the process is one that requires the resynthesis of ATP (Gazzaniga et al., 2002), one would expect creatine supplementation by elderly individuals to have a beneficial effect on working memory and long-term memory. This is particularly so as research has shown that the metabolism of the brain increases with age (Behzadi & Liu, 2005). Therefore, we hypothesized that creatine monohydrate supplementation by elderly individuals would have a beneficial effect on the performance of working memory and long-term memory.

METHOD

Participants

The participants were healthy elderly people, mean age 76.4 (*SD* = 8.48) years who regularly attended a day center. Participants were divided into two groups, Group 1 (*n* = 8 males, 7 females) and Group 2 (*n* = 8 males, 9 females), dependent on the days that they attended the center. There were no significant differences between groups for age or educational attainment. They were all volunteers and signed informed consent forms. They were informed that they could withdraw from the experiment at any time. Participants were screened for degenerative diseases and eyesight and hearing problems which may have affected performance of the cognitive tasks prior to taking part in the experiment. The study was approved by the ethical committees of the University of Chichester and the Poznan University of Medical Science.

Cognitive Tests

Participants undertook a random number generation test (Baddeley et al., 1998). They were instructed to call out numbers from one to nine in a totally random fashion. They were told to imagine how they would have to respond if they were guided by picking numbers out of a hat. This is in line with instructions given in other random generation tests (see Brugger, 1997). The test lasted for 1 min. Participants had to make a response every second. A metronome was used to provide timing. The dependent variable was the random number generation index, devised by Evans (1978). The results were analyzed by the computer program RgCalc (Nico Mak Computing, Bristol, CT) (Towse & Neil, 1998). Towse and Valentine (1997) have shown that there is no learning effect in random generation tasks when feedback is not supplied.

Verbal and spatial short-term memory tests were also carried out. There were two tests in each condition, requiring either forward or backward recall. The verbal tests were those of Baddeley et al. (1998) and the spatial tests were variations of the Corsi Block Tapping test (Corsi, 1971). In the forward recall test, the experimenter read out a series of numbers and the participant had to repeat them immediately. The protocol for the backward recall test was identical except that the participant had to recall the numbers in reverse order. The experimenter began with three numbers and increased the amount by one every trial. The dependent variable was the amount of numbers repeated in the final successful trial. In the spatial recall tests, participants sat facing a series of eight blocks (5 cms^3) which were 10 cms apart in a line. The protocol was the same as for the number recall tests except that both the experimenter and the participant pointed to the blocks rather than speaking. The dependent variable was the number of blocks repeated in the final successful trial.

Intra-class test of reliability by analysis of variance showed these tests to be highly reliable, $R \geq 0.92$ (McMorris et al., 2006b).

Participants also undertook a long-term memory test, which was similar to that used by Cian et al. (2001). Participants were shown 10 photographs of people with an occupation written beneath the photograph. One hour later they were shown 20 photographs, which included the 10 originals. In some of the false cues the face was correct but not the occupation. They were told to state which were the originals. Participants were told that all 10 may be in the selection or none at all. One point was given if the face was recognized and two points if both the face and occupation were correctly recalled.

Procedure

All participants undertook a habituation period on the cognitive tasks. They then took the tests in order to establish a baseline level. Following completion of the baseline tests, Group 1 were given a placebo (Maxijoule, SHS International, Liverpool, UK) for 1 week followed by a further week on pure creatine (Creapure, Deguss AG, Düsseldorf, Germany), both of which were purchased from the manufacturers. Group 2 were given the placebo for 2 weeks. Participants took 5 g of creatine monohydrate or placebo, as appropriate, in liquid form, freshly dissolved in water, four times a day. As treatment only took 2 weeks and the dosages of placebo and creatine were acute, there is little chance of side effects, e.g., weight gain, which would alert subjects to the treatment they were receiving, being manifested. This regimen is in line with that of Mielcarz et al. (2005), who demonstrated a significant effect of creatine supplementation on the physical performance of elderly individuals. The study was double-blind.

Statistical Analysis

As there were significant differences between groups at baseline, on the random number and backward spatial recall tests, and because we were not interested in interaction effects, planned comparisons were used rather than group × time analysis of variance (ANOVA) to examine the data. Within group differences were measured by separate one-way ANOVAs and follow up student *t*-tests with the Bonferroni correction factor. This meant that probability was set at $p < 0.02$. As there were significant differences between groups at baseline, intergroup differences at weeks 1 and 2 were compared using changes in scores from those at baseline (Δ scores) rather than actual scores. Student *t*-tests with the Bonferroni correction factor were calculated. This meant that probability was set at $p < 0.03$. For ANOVA results effect size was measured by η^2 and for *t*-tests by Cohen's *d*. Sphericity was examined by Mauchly's test and, if appropriate, the Huyn-Feldt epsilon correction factor was applied.

RESULTS

Table 1 shows the mean (*SE*) scores for random number generation for each group at baseline, and weeks 1 and 2. There were no within group differences. Δ scores at week 1 and week 2 for group 1 were 0.008 (*SE* = 0.03) and 0.058 (*SE* = 0.02), respectively. Δ scores for group 2 at week 1 were 0.017 (*SE* = 0.01) and at week 2 they were 0.001 (*SE* = 0.02). There were no significant between-group differences.

Table 2 shows the mean (*SE*) scores for each group on each of the recall tests at baseline and in weeks 1 and 2. One-way ANOVA showed that for forward number recall, Group 1 demonstrated a significant effect for time ($F_{2,22} = 3.67$, $p < 0.05$, $\eta^2 = 0.25$). Follow up *t*-tests with the Bonferroni correction factor found that baseline performance differed significantly from that at week 2 ($t_{11} = 2.35$, $p < 0.02$, d = 0.68). There were no other significant results although differences in performance at weeks 1 and 2 approached

TABLE 1. Mean (*SE*) scores for both groups, at each time period, on the random number generation test

GROUP 1TIME			GROUP 2 TIME		
BASE	ONE	TWO	BASE	ONE	TWO
0.273	0.299	0.331	0.255	0.272	0.256
(0.02)	(0.03)	(0.02)	(0.01)	(0.01)	(0.02)

Note. Random number generation is scored on the random number generation index (see Evans, 1978).

TABLE 2. Mean (*SE*) scores both groups, at each time period, on the number recall tests

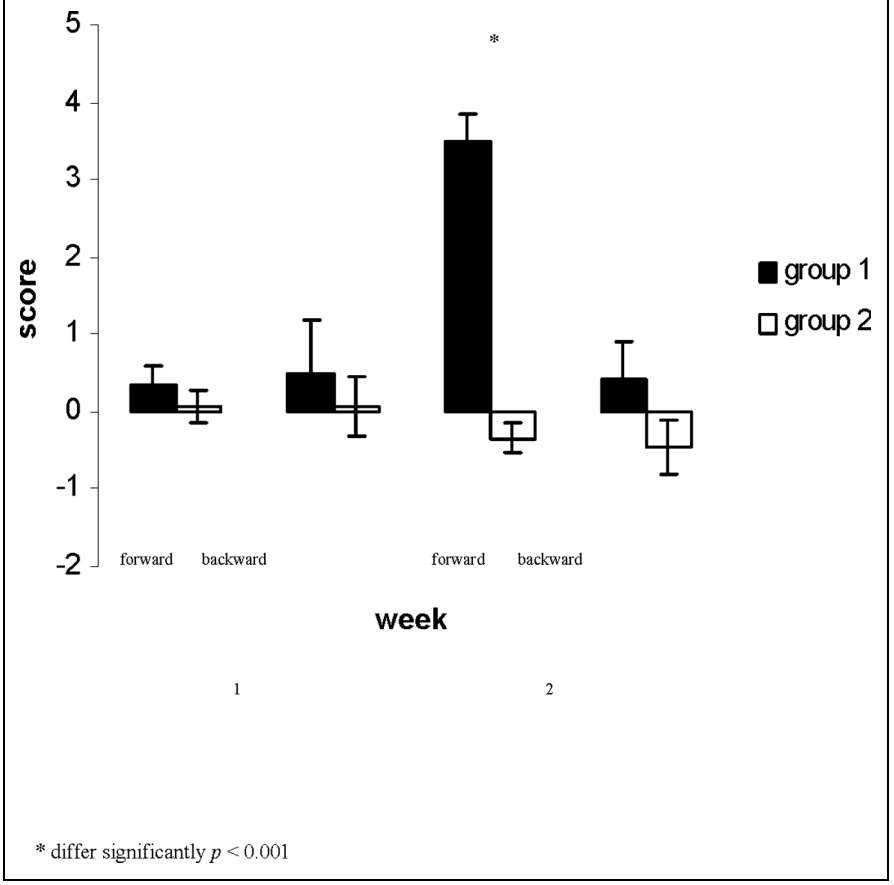
	GROUP 1 TIME			GROUP 2 TIME		
	BASE	ONE	TWO	BASE	ONE	TWO
Forward number	4.50 (0.19)	4.83 (0.17)	5.17* (0.21)	4.29 (0.14)	4.35 (0.17)	4.18 (0.13)
Backward number	3.08 (0.31)	3.58 (0.68)	3.42 (0.36)	2.76 (0.26)	2.82 (0.27)	2.29 (0.32)
Forward spatial	3.67 (0.40)	3.92 (0.43)	4.50 (0.29)	3.88 (0.17)	3.76 (0.29)	3.53 (0.12)
Backward spatial	2.33 (0.41)	2.67 (0.59)	4.08** (0.23)	3.41 (0.17)	2.94 (0.37)	3.06 (0.22)

Note. *differs significantly from baseline scores $p < 0.02$.
**differs significantly from baseline and week one $p < 0.02$.

significance with a moderate effect size (t_{11} = 2.77, p = 0.05, d = 0.51). Figure 1 shows the mean (*SE*) Δ scores for both forward and backward number recall. For forward recall, Δ scores differed significantly between groups at week 2 (t_{27} = 3.85, p < 0.001, d = 1.8). Δ forward number recall scores at week 1 did not differ significantly from one another. For backward number recall, there were no significant within-group effects and no significant differences between groups for Δ scores at either time period.

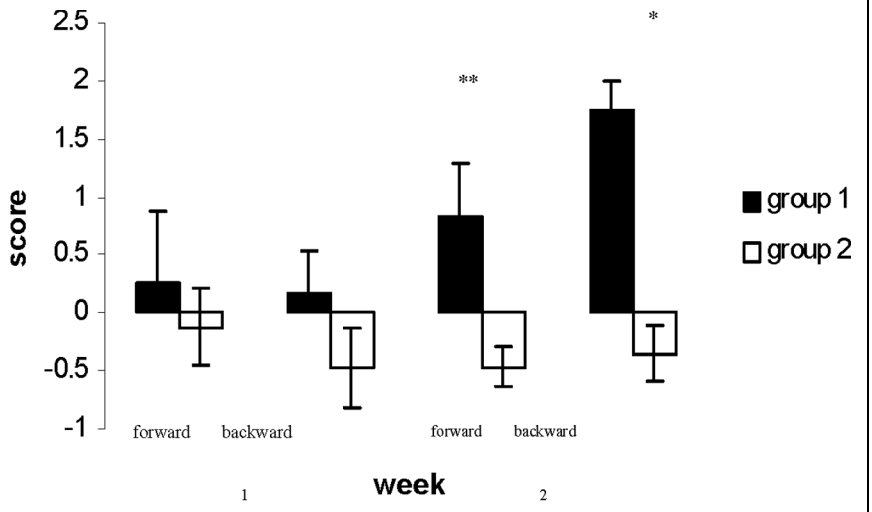
There were no significant within-group effects of time for forward spatial recall for either group. Figure 2 shows the mean (*SE*) Δ scores for both forward and backward spatial recall. For forward spatial recall, Δ scores differed significantly between groups at week 2 (t_{27} = 3.00, p < .0.005, d = 0.99). Δ scores did not differ significantly at week 1. For backward spatial recall, one-way ANOVA demonstrated a significant within-group effect

FIGURE 1. Mean (*SE*) Δ scores at weeks 1 and 2 for both groups on the forward and backward number recall tests.



* differ significantly p < 0.001

FIGURE 2. Mean (*SE*) Δ scores at weeks 1 and 2 for both groups on the forward and backward spatial recall tests.



** differ significantly $p < 0.005$
* differ significantly $p < 0.001$

($F_{2,22}$ = 13.72, $p < 0.001$, $\eta^2 = 0.56$) for Group 1. Follow up *t*-tests with Bonferroni correction factor showed that performance at week 2 differed significantly from baseline (t_{11} = 7.00, $p < 0.001$, d = 2.01) and week 1 (t_{11} = 3.26, $p < 0.005$, d = 0.94). There were no significant effects for Group 2. Δ backward spatial recall scores at week 2 differed significantly (t_{27} = 5.90, $p < 0.001$, d = 1.5). There was no significant difference at week 1.

Table 3 shows the mean (*SE*) scores for each group on the long-term memory test at baseline and weeks 1 and 2. One-way ANOVA demonstrated a signif-

TABLE 3. Mean (SE) for both groups, at each time period, on the long-term memory test

GROUP 1TIME			GROUP 2 TIME		
BASE	ONE	TWO	BASE	ONE	TWO
12.92	13.75	15.25**	13.24	14.47	13.06
(1.43)	(1.49)	(1.49)	(0.74)	(0.87)	(0.91)

Note. **differs significantly from baseline and week one $p < 0.02$.

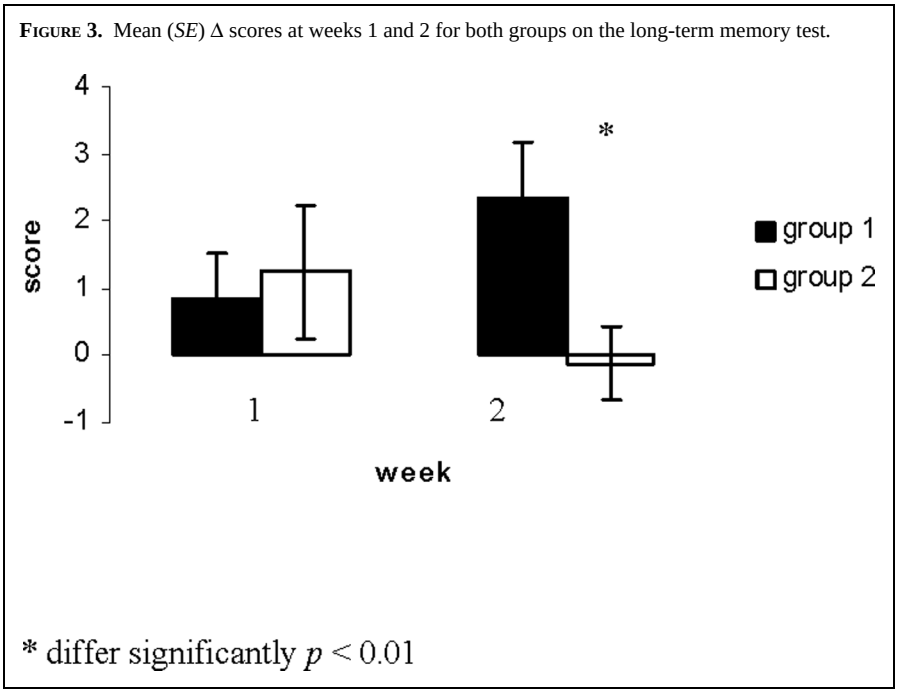


FIGURE 3. Mean (*SE*) Δ scores at weeks 1 and 2 for both groups on the long-term memory test.

icant effect of time for Group 1 ($F_{2,22} = 6.24$, $p < 0.01$, $\eta^2 = 0.36$). Follow up *t*-tests with Bonferroni correction factor found that performance at week 2 differed significantly from that at baseline ($t_{11} = 2.82$, $p < 0.01$, d = 0.81) and week 1 ($t_{11} = 3.59$, $p < 0.005$, d = 1.03). There were no significant effects of time for Group 2. Figure 3 shows mean (*SE*) Δ scores for each group. Δ scores differed between groups at week 2 ($t_{27} = 2.54$, $p < 0.01$, d = 0.85) but not at week 1.

DISCUSSION

The results from this study show that creatine monohydrate supplementation does aid performance of cognitive tasks but not all of the tasks were affected. Supplementation had no significant effect on random number generation. This is surprising as this is a central executive task requiring recruitment of larger areas of the brain than the other tasks (Smith & Jonides, 1999) and is considered to be more difficult than the recall and long-term memory tasks (Baddeley et al., 1998). Thus it is expected that this will require more energy than those tasks. However, there is no empirical evidence for this assumption and a larger area does not necessarily mean a greater need for energy. Future research should examine the differences in energy output by the different parts of the brain that are activated during these tasks. Nevertheless, it is difficult to see why the central executive task was not affected

while the phonological loop and visuospatial sketchpad tasks were. It may be that the increases in brain creatine were insufficient for a task that activates such large areas of the brain. If this were so, it may also explain the somewhat contradictory results for the number and spatial recall tasks.

Results from the forward number recall test demonstrated a significantly positive effect of creatine supplementation on performance, with Group 1 showing within group effects and a better Δ score than Group 2 at week 2. Backward recall results were not significantly affected. The backward task requires the individual to not only hold the numbers in short-term memory but also to reorganize them; whereas forward recall only requires holding the information in short-tern memory. Backward recall is, therefore, considered to be the more difficult task. Given this, it is not surprising to find that Sun et al. (2005) have shown that backward number recall activates larger areas of the brain than does forward number recall.

For the spatial recall tasks, both forward and backward recall benefited significantly from creatine supplementation. Group 1 showed significantly better Δ scores at week 2 for both forward and backward recall. Group 1 also demonstrated a significant within-group effect for backward recall with performance in the creatine condition being better than that at baseline and in the placebo condition. The most likely reason for differences in results for spatial recall compared to number recall is that these tasks are actually less demanding than the number recall tasks because the individual needs to hold less in short-term memory as the blocks are in front of them throughout the test (Brugger, 1997). It should also be remembered that the spatial recall tasks are primarily right-hemisphere tasks, while number recall is a left-hemisphere task (Smith & Jonides, 1999), which may affect results. It should be noted that creatine supplementation does not affect all areas of the brain in the same way (Dechent et al., 1999), which may account for our results.

For the long-term memory task, significant within-group effects were shown for Group 1 and Δ scores at week 2 differed significantly between groups with Group 1 being superior. This task requires primarily right-hemisphere activity similar to the spatial recall tasks. Nevertheless, considerable energy is required for consolidation in the hippocampus and recall from many areas of the neocortex by the dorsolateral prefrontal cortex. However, it is likely that it does not require as much energy as the central executive tasks but this is merely conjecture.

The explanation for our data, so far proposed, has assumed that the effect of creatine supplementation is to make ATP resynthesis more efficient. There is no doubt that elderly people require more energy, in order to carry out cognitive tasks, than do younger individuals (Behzadi & Liu, 2005; Toescu, 2005). However, magnetic resonance spectroscopy studies with humans have tended to show that creatine levels in the brain actually increase with age (e.g., Pfefferbaum et al., 1999) in healthy individuals. It

does not appear that the increase in brain creatine is sufficient to make up for general brain deterioration. Nevertheless, one cannot rule out the possibility that energy supply is not the major issue with regard to the facilitating effect of creatine supplementation in the elderly.

An alternative explanation is provided by the claim of Ellis and Rosenfeld (2004) that the positive effects of creatine supplementation are due to the fact that the presence of creatine improves mitochondrial membrane stimulation, intracellular handling, antioxidant mechanisms, and glutamate reuptake in synaptic vesicles, with a resultant neuroprotective effect on several chemicals in the brain, particularly dopamine and glutamate. Research with individuals with Parkinson's disease (see Fernandez-Espejo, 2004) has shown that creatine supplementation has resulted in increased concentrations of brain dopamine. Similar research with Huntington's disease patients (Bender et al., 2005) has demonstrated a lowering of glutamate concentrations suggesting greater reuptake by synaptic vesicles. This would aid cognition because dopamine is a neurotransmitter that plays a major role in working memory tasks, while glutamate is an excitatory neurotransmitter that at high levels can disrupt cognitive performance due to excitoxicity of neurons. This is an area that requires more research.

In conclusion, we can say that creatine monohydrate supplementation had a beneficial effect on some, but not all, of the cognitive tasks used in this study. It may be that task complexity and the areas of the brain activated during the tasks may have an effect on the ability of creatine supplementation to aid performance. Whether the energy required is due to the volume of the area or the amount of energy required by any specific area is debatable. Despite the findings of this study, we should not dismiss the possibilities of creatine supplementation having an effect on random number generation tasks and the more difficult backward number recall task. The sample size is small and creatine loading in this study was acute. It is possible that longer periods of loading would be more beneficial and aid even the complex central executive tasks. Moreover, the way in which creatine supplementation aids cognitive performance in elderly individuals requires some attention. The argument of whether it is due to aiding the resynthesis of ATP or due to its role as a neuroprotector, with regard to glutamate and dopamine, should be addressed.

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