Can Creatine Combat the Mental Fatigue–associated Decrease in Visuomotor Skills?

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ABSTRACT

VAN CUTSEM, J., B. ROELANDS, B. PLUYM, B. TASSIGNON, J. VERSCHUEREN, K. DE PAUW, and R. MEEUSEN. Can Creatine Combat the Mental Fatigue–associated Decrease in Visuomotor Skills? *Med. Sci. Sports Exerc.*, Vol. 52, No. 1, pp. 120–130, 2020. **Purpose:** The importance of the brain in sports was recently confirmed by the negative effect of mental fatigue (MF) on sport-specific psychomotor skills. Creatine supplementation improves strength but can also improve cognitive functioning. To explore the role of creatine in combating MF, we evaluated whether creatine supplementation counteracts the MF-associated impairment in sport-specific psychomotor skills. **Methods:** In 23°C, 14 healthy participants (4 females, 10 males; mean ± SD, age = 24 ± 3 yr, mass = 74 ± 13 kg, height = 179 ± 9 cm) performed a 90-min mentally fatiguing task (counterbalanced, crossover, and double-blinded; i.e., Stroop task) in two different conditions: after a 7-d creatine supplementation (CR; 20 $g \cdot d^{-1}$) and after a 7-d calcium lactate supplementation (placebo [PLAC]), separated by a 5-wk washout. In both conditions, a 7-min sport-specific visuomotor task, a dynamic handgrip strength endurance task, and a 3-min Flanker task was performed before and after the mentally fatiguing task. Physiological and perceptual responses were measured throughout the protocol. **Results:** Handgrip strength endurance was higher in CR compared with PLAC ($P = 0.022$). MF impaired visuomotor response time (+4.4%; $P = 0.022$) and Flanker accuracy (−5.0%; $P = 0.009$) in both conditions. Accuracy on the Stroop task was higher in CR compared with PLAC (+4.9%; $P = 0.026$). Within the perceptual and physiological parameters, only motivation and vigor ($P \leq 0.027$) were lower in CR compared with PLAC. **Conclusion:** Creatine supplementation improved physical (strength endurance) and prolonged cognitive (Stroop accuracy) performance, yet it did not combat MF-induced impairments in short sport-specific psychomotor or cognitive (Flanker) performance. These results warrant further investigation in the potential role of creatine in combating the MF-associated decrements in prolonged (e.g., 90-min soccer game) sport performance and suggest a role of brain phosphocreatine in MF. **Key Words:** CREATINE SUPPLEMENTATION, PHOSPHOCREATINE, MENTAL EXERTION, COGNITIVE FATIGUE, VISUOMOTOR RESPONSE TIME, COGNITIVE PERFORMANCE

In many sports, athletes need to perform in a dynamically changing, unpredictable, and externally paced environment. As such, the outcome of many sport events is greatly determined by the athlete's cognitive capacity to make accurate decisions and execute them accordingly (i.e., psychomotor skills). Recently, the importance of cognitive capacity in sport performance has been further substantiated by a line of research demonstrating the negative effect of mental fatigue (MF) on physical performance (1). MF is a psychobiological state induced by prolonged exertion that impairs endurance performance and sport-specific psychomotor skills (1,2). It seems that these impairments are not mediated by a change in traditional physiological systems known to support physical performance (e.g., heart rate [HR], blood lactate, oxygen uptake, cardiac output, and maximal aerobic capacity) (1,2). As such, a prominent role of the brain in these MF-associated impairments became evident.

This triggered the interest to determine more specifically which brain-related mechanisms could mediate the impairments caused by MF. In an attempt to account for the MF-induced performance impairments, several models have been proposed (3). Two major hypotheses are put forward within these models: 1) a depletable physiological resource and 2) an effort-based decision in which effort arises from the opportunity costs (i.e., the value of the next best alternative to the task at hand) and will shift attention away from the task at hand. Both hypotheses have the assumption that performance impairments caused by a preceding mentally fatiguing task occur because of similarity across the mentally fatiguing task and the subsequent task (e.g., similar executive function systems that are engaged). This similarity will eventually lead to decrements in performance on the second task. The hypothesis that a depleted physiological resource (e.g., glucose [GLUC]) could account

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for this performance decrement on the second task is however often discounted based on arguments that point out that it is highly unlikely that GLUC is this resource (3,4). While supporting this critique on the depletable physiological resource account, the relevance of some of these arguments is questionable (e.g., based on whole brain metabolism measures (5)). To more properly discuss the plausibility of a depletable physiological resource account in MF, 1) other candidate physiological resources should be assessed, and 2) these resources should be considered more locally (i.e., local neuronal assemblies in the brain [6]).

In the unstimulated brain, energy is primarily supplied by the oxidation of GLUC (7). GLUC is transported across the blood–brain barrier, enters astrocytes, and is converted into lactate by glycolysis. Lactate is subsequently released into the extracellular space, taken up in neurons and oxidized. During slow spiking rates (e.g., rest), the glial (e.g., astrocytes) adenosine triphosphate (ATP) pool synthesis is closely matched with the neuronal ATP pool synthesis. However, during faster spiking rates (e.g., a cognitive task), rapid neuronal bursts put a high-energy demand on the glia. The glia need to rapidly clear released neurotransmitters and buffer changes in sodium (Na) and potassium (K) fluxes associated with neuronal activity. In this case, the glial ATP pool synthesis is not fast enough to restore glial ATP levels in between spikes and is forced to use other energy production pathways (7). A first energy mechanism that will be addressed when glial energy demand exceeds supply is the phosphocreatine (PCr) system. However, this system only has a short-term capacity to provide additional ATP, and as such, a drop in PCr will quickly follow. Once the PCr system's capacity is reduced, other mechanisms will attempt to increase the glial energy supply (e.g., the glycogen shunt and/or an enhancement of nonoxidative glycolysis) (7). A study by Sappey-Marinier et al. (8) showed that prolonged activation of the brain visual cortex was associated with a diminished brain PCr concentration and a concomitant decrease in stimulus-related brain activity (8).

A decrease in stimulus-related brain activity is also associated with the occurrence of MF (9,10). This indicates that brain PCr concentration may play a role in MF. To assess whether a drop in PCr has a significant role, creatine could be supplemented. Creatine administration has been reported to successfully increase creatine content in the human brain (11–13). Thus, if the drop in PCr has a role in the occurrence of MF, then an increase in PCr due to creatine supplementation should be able to increase resistance to MF. Multiple studies have already evaluated the effect of creatine supplementation on cognitive performance (see review of Rae et al. [14]), and overall, it is clear creatine enhances cognitive performance. Watanabe et al. (12) evaluated the effects of creatine on MF. Dietary supplementation of creatine (8 $g \cdot d^{-1}$ for 5 d) reduced MF when participants repeatedly performed a simple mathematical calculation. They speculated that increased capacity of the PCr system led to decreased accumulation of lactate generated by anaerobic glycolysis, which caused less MF (12). Watanabe et al. (12) also measured cerebral hemoglobin oxygenation and observed indications for increased oxygen utilization in the brain after creatine supplementation. In addition, two studies of McMorris et al. (15,16) on creatine supplementation and sleep deprivation also pointed toward a positive effect of creatine on MF.

Despite these first studies on the interaction between creatine and MF (12,15,16), the role of a possible drop in PCr in the occurrence of MF is still unclear. Therefore, the aim of this study was to determine the effect of PCr supplementation on MF and its negative effects on sport-specific psychomotor skills. On the basis of the results of Watanabe et al. (12) and McMorris et al. (15,16), we hypothesized that a 7-d creatine supplementation protocol would postpone the occurrence of MF and improve sport-specific psychomotor skills in a mentally fatigued state.

METHODS

Participants and ethical approval. An *a priori* sample size calculation based on the results reported in the study of Rae et al. (17) (reported effect size on cognitive performance = 1.01) showed that a total of 14 participants are needed to observe the effect of creatine supplementation on performance. Sixteen participants volunteered to participate in the present study, two dropped out due to personal time schedules interfering with participation in the study. Fourteen non–color blind participants (4 females, 10 males; mean ± SD, age = 24 ± 3 yr, mass = 74 ± 13 kg, height = 179 ± 9 cm) were included in the present study. None of the participants had any known mental or somatic disorder, and all were cataloged as low to moderately active according to the short form of the International Physical Activity Questionnaire (18). This criterion was included based on the assumption that a lower physical activity profile maximizes the effect of creatine supplementation on brain creatine concentration (19). Each participant gave written informed consent before the study. Experimental protocol and procedures were approved by the Research Council of the Vrije Universiteit Brussel, Belgium. All participants were given written instructions describing all procedures related to the study but were naive of its aims and hypotheses. Participants were informed that the purpose of the study was to investigate the effect of two (creatine and calcium lactate) potentially performance-enhancing substances and were debriefed after completing all trials.

Experimental protocol. The participants were asked to return to the laboratory for three consecutive trials (crossover design). The first trial was a 60-min familiarization trial to get to know the routine and to avoid learning effects. Participants completed all procedures as if it was an experimental trial (see Fig. 1), except for the 90-min cognitive task. We determined the participants' maximal cognitive capacity with a modified Stroop task, divided in blocks of 96 stimuli. After each block, the accuracy was calculated. When the accuracy was higher than 85%, the difficulty of the Stroop task was increased by decreasing the stimulus presentation time (SPT). If the accuracy was lower than 85%, this block was considered

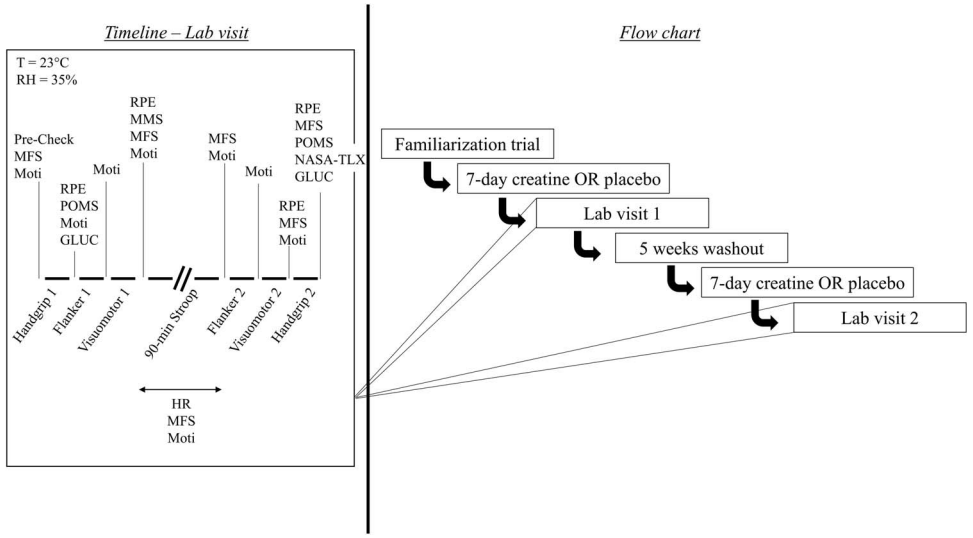

FIGURE 1—Schematic overview of the protocol. T, ambient temperature; RH, relative humidity; Pre-Check, pretrial checklist; MFS, MF visual analog scale; Moti, motivation visual analog scale; NASA-TLX, National Aeronautics and Space Administration Task Load Index.

as an "error" and the participant had to redo the block without changing the SPT. The first block had an SPT of 1500 ms and had the main objective to get familiar with the task. When the required accuracy was achieved, the SPT was decreased in the following order: 1100, 900, 700, 650, 600, 550 ms, etc., to determine the individual cognitive capacity. Before the start of each block, the participants were able to take a break if they liked. When the participant made three errors in a row, or five errors during the whole trial, the trial was considered as completed and ended. The SPT of the last successfully completed block was considered as the maximum capacity of that individual. Preceding the beginning of the familiarization trial, participants had to read the informed consent and got a thorough explanation of what was expected from them; afterward, they had the possibility to ask questions. The mean maximal cognitive capacity was 911 ± 41 ms.

The familiarization trial was followed by two interventional trials in a randomized counterbalanced order. Participants had to visit the laboratory twice after a 7-d nutritional intervention (creatine trial [CR] or calcium lactate trial [PLAC]; see Supplementation Protocol and Nutritional Intervention section) within a period of 6 wk. This was because of the 5-wk washout period between both supplementation periods. Participants and researchers involved in data collection were blinded to the nutritional intervention. Each laboratory visit took approximately 2 h 30 min, and participants reported themselves at the same time of day. Before starting a trial, compliance with instructions (see Restrictions and Prohibitions for the Participants section) was assessed with a checklist. Participants were seated in a comfortable chair in a sound-insulated laboratory, in thermoneutral conditions (23°C, humidity 35%). To determine the effect of creatine supplementation on cognitive and physical performance, all trials began with a baseline handgrip strength endurance task (~3 min: see Strength Endurance Task section). After completing the baseline strength endurance task, participants had to complete two more tasks, a baseline Flanker task (duration ~3 min; see Flanker task section) and a baseline sport-specific visuomotor task (duration ~7 min; see Sport-Specific Visuomotor Task section), followed by a 90-min Stroop task (see Stroop Task section). Immediately (20 s) after completion of the 90-min Stroop task, the same 3-min Flanker task was performed. Immediately (~2 min) thereafter, a second sport-specific visuomotor task and strength endurance task was performed (see Fig. 1).

Restrictions and prohibitions for the participants. Participants were asked not to change eating, activity, or sleeping (guideline to sleep for at least 7 $h \cdot d^{-1}$) patterns abruptly during the study period (i.e., during supplementation of creatine and placebo) and to limit alcohol intake to no more than two drinks every 24 h. A drink was defined as 330 mL of beer, a glass of wine, or 30 mL of hard or distilled alcohol. The day before and from each laboratory visit, the participants were expected to sleep for at least 7 h, refrain from the consumption of caffeine and alcohol, and not practice vigorous physical activity. In addition, participants were asked to have a similar breakfast and cognitive load the morning of each laboratory visit. The use of any kind of medicinal products during and between the trials was prohibited. If participants could not meet these standards (assessed with a checklist), they were excluded from the study.

Supplementation protocol and nutritional intervention. Supplementation was performed in a randomized, counterbalanced, double-blind, crossover design. A creatine (commercially available; Sportimaxx) and placebo (calcium lactate; Sterop) supplementation regime was conducted for 7 d, separated by a washout period of 5 wk. Participants were instructed to take in 20 tablets throughout the day at four equally spaced intervals, ensuring that consumption respective to meal times was consistent (8, 12, 16, and 20 h). Creatine tablets contained 1 g of creatine monohydrate/tablet, equating to a daily dose of 20 g, 0.53 g fiber, and 0.01 g fat. Placebo tablets contained 39 mg of elemental calcium/tablet, equating to a daily dose of 0.780 g, anticaking agents (magnesium stearate,

glycerol dibehenate, and talc), a carrier (povidone CL), and a firming agent (povidone K30). Participants did not take creatine or placebo on the day of the test. To assess the successfulness of the participant-blinding method, participants were asked, after completion of all trials, to guess when they supplemented creatine and when calcium lactate (i.e., placebo). A 7-d creatine supplementation protocol (20 $g \cdot d^{-1}$) has already been shown to successfully augment (+6%) brain creatine (13).

Sport-specific visuomotor task. To assess psychomotor performance, a visuomotor task was developed with Fitlight hardware and software (http://www.fitlighttraining.com/). Seven LED powered lights were set up against a wall and illuminated for 2 s, one after the other in a set sequence (see Fig. 2). These LED lights were colored, similar to the Stroop stimuli, red, blue, green, or yellow. If a LED light turned red, green or yellow (i.e., simple stimuli), participants had to put out the LED light as fast as possible by passing before the LED light with the left or right hand within a range of 5 cm. However, if a LED light turned blue (i.e., complex stimulus), participants were instructed not to respond to the stimulus on the wall. Instead, they had to turn around and put out another LED light lying behind them on the floor (1 m 50 cm; no. 8; see Fig. 2). After each stimulus, participants were instructed to return to their starting position (perpendicular to LED light no. 1, 1 m 20 cm away from the wall, and with both feet ~30 cm apart and on the same line), which was indicated on the floor, and focus again on the fixation cross (see Fig. 2). Each color was presented 16 times, yielding a total of 64 stimuli. The interstimulus time varied between 3, 4, 5, and 6 s, and each interstimulus time was randomly used 16 times. Total task duration was approximately 6 min 30 s. To avoid learning effects, each visuomotor task was started randomly somewhere within the preprogrammed sequence. Response times (RT) were collected to assess performance.

Strength endurance task. A dynamic handgrip strength endurance task was included in the present study 1) to evaluate the effect of MF on this endurance performance and 2) to serve as a manipulation check for successful creatine supplementation (20). During the familiarization trial, a hydraulic hand dynamometer (Model SH5001; Saehan Corp. Masan, Korea) was adjusted for individual hand size, and a height-adjustable chair was set up so participants could adopt a seated, upright position with their feet supported, shoulders adducted and neutrally rotated, elbow flexed at 90°, the forearm in neutral position, and the wrist at extension between 0° and 30° (21). These settings were replicated during both following intervention trials. The testing protocol consisted of 12 repeated maximal isometric contractions for 3 s, with a 5-s rest between repetitions. This protocol was preceded by 5 submaximal—not capable of inducing muscle fatigue—handgrip contractions and was first completed with the dominant and 5 min thereafter with the nondominant hand (all participants were right-handed). The protocol has been shown valid to assess handgrip strength endurance (21), a performance measure that is known to improve

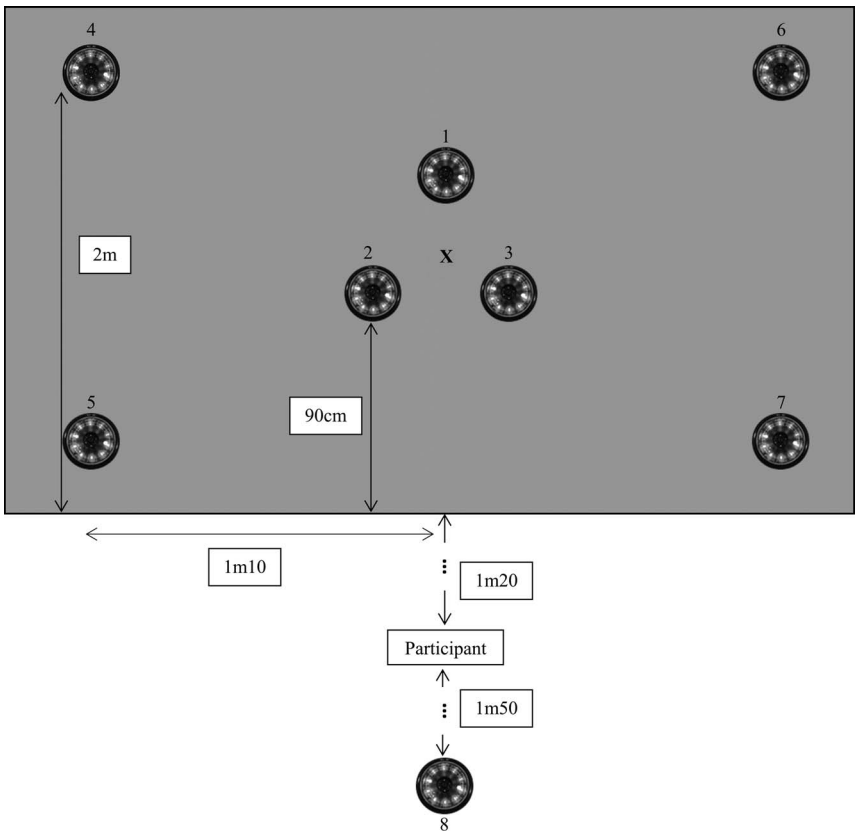

FIGURE 2—Overview of the visuomotor task. ⊛ = LED light.

following creatine supplementation (20). During the protocol, participants were required not to perform any other movement than maximally squeezing their hand. The tested arm was positioned on a table to support the weight of the dynamometer, and the dynamometers' base rested on the table while the handle rested on the middle of the four fingers. No encouragements or performance feedback were provided. For the evaluation of dynamic handgrip strength endurance, we used percentage change in force output using the following equation: [(the mean of the last 3 repetitions/the mean of the first 3 repetitions) × 100]. This index of dynamic handgrip strength endurance has been shown to have good reliability for the 12-repetition protocol and is recommended for the determination of dynamic handgrip strength endurance (21).

Flanker task. The Flanker task was included in the present study to assess the effect of MF on cognitive performance independent from time on task. In the Flanker task, all cues were incongruent, meaning the flanking arrows pointed in the opposite direction as the target middle arrow (e.g., < < > < <), requiring a great level of inhibitory control over the flanker arrows to execute an accurate response. Each array of arrows was focally presented in white text for 200 ms on a black background with a variable interstimulus interval of 1000, 1200, 1400, or 1600 ms. One hundred and twenty trials were presented randomly with right and left target arrows occurring with equal probability. Total Flanker task duration was approximately 3 min. Participants were instructed to respond as quickly and accurately as possible to the direction of the target middle arrow while ignoring two flankers on each side. The second Flanker task was performed exactly 20 s after completion of the Stroop task. To assess performance on the Flanker task, accuracy and RT were collected. Because of software problems, the performance results of one participant were not saved, and the statistical analysis on Flanker performance was performed with $n = 13$.

Stroop task. To induce MF, a modified Stroop task (22) of 90 min, partitioned in eight blocks of 252 stimuli, was performed by the participants. This 90-min task was continuous with no rest breaks (i.e., participants had no knowledge of the existence of the eight task blocks). The inclusion of the eight task blocks/epochs allows the researcher to examine performance impairment (i.e., accuracy and RT) as a function of time on task, which is a behavioral indicator of cognitive fatigue (1,23). The Stroop task requires inhibition and sustained attention on controlled processes (24). In this task, four colored words ("red," "blue," "green," and "yellow") were presented one at a time on a computer screen. The participants were required to indicate the color of the word (i.e., "color" stimuli), ignoring the meaning of the word itself. If, however, the ink color was red, the button to be pressed was the button linked to the real meaning of the word, not the ink color (i.e., "meaning" stimuli). The word presented and its ink color were randomly selected by the computer (100% incongruent), with all incongruent word–color combinations being equally common (meaning, in each block, 63 words were presented in the color red, yellow, green, and blue). Each word was presented on screen in 34-point font for 1000 ms with a variable interstimulus interval of 1100, 1500, or 1900 ms, with each interstimulus interval being equally common. Participants were instructed to respond as quickly and accurately as possible. Performance was assessed similarly to the Flanker task (due to software problems, the performance results of one participant were not saved, and statistical analysis on Stroop performance was performed with $n = 13$), and a €50 reward for the best performance was given (taking into account mean accuracy and RT during both intervention trials). This should minimize the negative effects of poor motivation and disengagement on Stroop performance. Before each 90-min Stroop task, time-keeping devices such as watches and cell phones were removed, and during the task, participants did not receive any feedback on performance or time lapsed. Participants were seated in a comfortable chair in a sound-insulated room.

Physiological and psychological assessment. During the 90-min Stroop task, participants were equipped with an HR monitor (Polar, RS400) that enabled us to record HR continuously. Before and after the entire protocol, GLUC was measured (Bayer, Contour Next Link). Psychological assessment took place throughout the protocol (see Fig. 1) with the success motivation and intrinsic motivation scales (MMS) developed and validated by Matthews et al. (25), the POMS to assess mood, session RPE, and an MF and motivation VAS scale (0–100) to assess, respectively, MF and motivation (22). The MMS was filled in before the start of the Stroop task; each scale in the MMS consists of seven items (e.g., "I want to succeed on the task" and "I am concerned about not doing as well as I can") scored on a 5-point Likert scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = very much, 4 = extremely). Therefore, total scores for the MMS range between 0 and 28. The 32-item POMS scale was assessed at the beginning and at the end of the protocol and consists of five subscales: tension, depression, anger, fatigue, and vigor. All items have to be scored from 0 (not at all) to 4 (extremely). The higher the score on a category, the more participants feel this mood state is present. The questionnaire was translated into the native language of the participants (Dutch [26]). To monitor the load of performing the sport-specific visuomotor task and strength endurance task, a session RPE was taken after completion of each of those tasks. Participants were asked how heavy and strenuous the task was, whereafter they had to indicate a number from 6 to 20 ("6 = rest", "20 = maximal"). The scale low and high anchor points were established by comparing 6 with rest and 20 with the most strenuous exercise participants ever experienced. The MF VAS scale was assessed at the start of the protocol, before, during, and after the Stroop task and at the end of the protocol. This scale assessed how mentally fatigued the participant was feeling (MFS; "0 = not at all" to "100 = completely exhausted"). The motivation VAS scale was assessed before each task included in the protocol and during the Stroop task. This scale evaluated how motivated the participant was feeling toward all tasks (Moti; "0 = not at all" to "100 = extremely motivated"). In order for the participants to be able to keep their hands in place on the keyboard

during the Stroop task, participants had to give their answer (both for MFS and Moti) orally by announcing a number between 0 and 100. The National Aeronautics and Space Administration Task Load Index (NASA-TLX [27]) is composed of six subscales and was filled in after completion of the last strength endurance task. The NASA-TLX evaluated the subjective workload of the Stroop task.

Statistical analysis. All data are presented as mean ± SE unless stated otherwise. The Shapiro–Wilk test and the visual interpretation of histograms were used to test the normality of the data. Sphericity was verified by the Mauchly's test. When the assumption of sphericity was not met, the significance of *F*-ratios was adjusted with the Greenhouse–Geisser procedure. If data were not normally distributed (i.e., POMS), nonparametric Wilcoxon tests were used to observe the effect of condition and time. All other parameters (i.e., behavioral [Stroop RT, Stroop accuracy on the meaning stimuli, visuomotor RT, Flanker RT, and strength endurance], perceptual [MMS, MFS, Moti, NASA-TLX, and session RPE], and physiological [HR and GLUC]) were normally distributed or normally distributed after a square root transformation (i.e., accuracy on the Flanker task and on the color stimuli in Stroop task was subtracted from a constant factor [1.01] and subsequently square root transformed). The effect of condition and time on all normally distributed parameters, besides handgrip strength endurance, was assessed by a two-way repeated-measures ANOVA. Meaning that, specifically regarding the Stroop and visuomotor performance, the effect of condition and time was assessed in each type of stimulus. For handgrip strength endurance, hand dominance was included as an additional factor and a three-way repeated-measure ANOVA was conducted. If significant interaction effects were observed, subsequent repeated-measure ANOVA or paired-samples *t*-tests were performed to elucidate the main effect of condition and time. If no significant interaction effects were observed, main effects of condition and time were immediately observed and further interpreted through pairwise comparisons with Bonferroni correction. Significance was set at <0.05 for all analyses, which were conducted using the Statistical Package for the Social Sciences, version 25 (SPSS Inc., Chicago, IL).

RESULTS

Blinding the participants for the nutritional interventions seemed to be successful. After completion of all trials, only 5 out of 14 were able to correctly identify when they had supplemented creatine and when calcium lactate.

Cognitive Performance

Mentally fatiguing task. Transformed accuracy throughout the 90-min Stroop task on the color stimuli was improved in CR compared with PLAC ($F_{1, 12} = 6.6$, $P = 0.025$, $\eta_p^2 = 0.354$; see Fig. 3), a trend for an effect of time ($F_{3.1, 37.7} = 2.4$, $P = 0.081$, $\eta_p^2 = 0.166$; see Fig. 3), and no interaction effect between condition and time was observed. RT on the color stimuli was not affected by either condition or time. With regard to the meaning stimuli, neither accuracy nor RT was different between CR and PLAC. Participants were however getting faster in time on the meaning stimuli (first task epoch = 727 ± 18 ms, eighth task epoch = 692 ± 15 ms; $F_{2.8, 34.1} = 6.5$, $P = 0.002$, $\eta_p^2 = 0.351$). No effect of time on accuracy on the meaning stimuli was observed.

The maximal cognitive capacity of each participant was assessed in the familiarization trial with a modified Stroop task

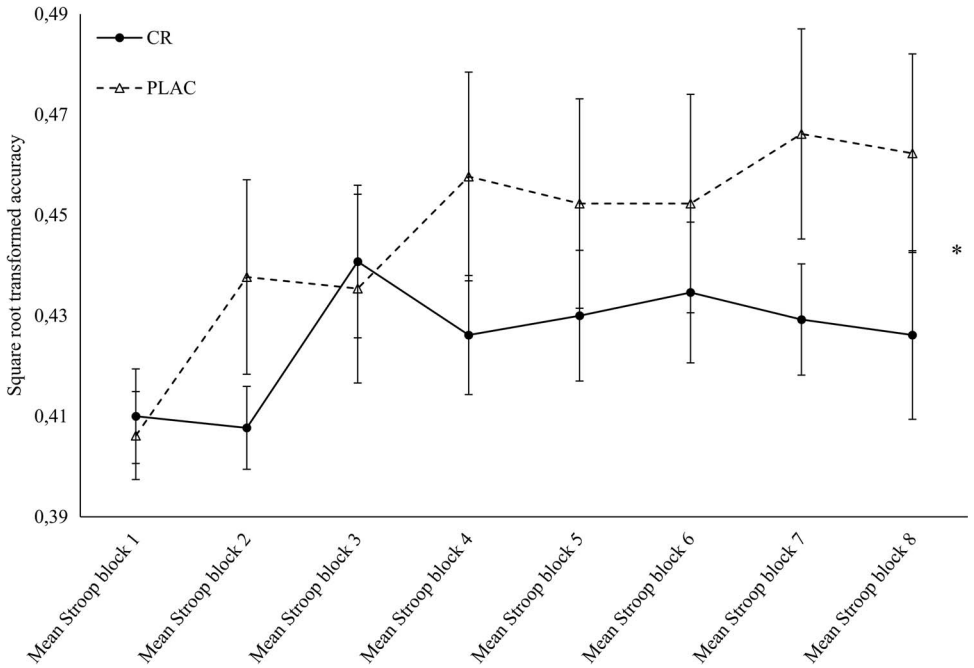

FIGURE 3—Stroop performance. Square root transformed accuracy on the color stimuli during the eight blocks of the Stroop task (higher transformed accuracy = lower performance). *Significant main effect of condition ($P < 0.05$). Data are presented as mean ± SE.

(see Experimental protocol section). Mean maximal cognitive capacity was 911 ± 41 ms. Including this parameter as a covariate in the repeated-measures analysis of the transformed accuracy on the color stimuli revealed that maximal cognitive capacity did not alter the observed effect of condition.

Flanker task. Transformed flanker accuracy increased (i.e., performance dropped; $F_{1,\ 12} = 9.7$, $P = 0.009$, $\eta_p^2 = 0.447$) after the mentally fatiguing task in both CR (pretrial = 0.26 ± 0.02, posttrial = 0.32 ± 0.03) and PLAC (pretrial = 0.25 ± 0.02, posttrial = 0.34 ± 0.03). RT did not differ in time or between conditions (CR = 379 ± 5 ms, PLAC = 378 ± 5 ms).

Strength Endurance

The effect of condition was different in the dominant and nondominant hand (condition–dominance interaction; $F_{1,\ 13} = 10.1$, $P = 0.007$, $\eta_p^2 = 0.436$). In the dominant hand, strength endurance did not differ between conditions, whereas in the nondominant hand, it was higher in CR compared with PLAC (last 3 reps/first 3 reps × 100: CR = 84% ± 2%, PLAC = 79.5% ± 1.9%, $P = 0.022$, $\eta_p^2 = 0.344$; see Table 1), and no effect of the mentally fatiguing task was however observed. An additional follow-up test to assess a possible condition effect on the mean of the first 3 repetitions demonstrated participants started the endurance protocol at a similar maximal handgrip level in both conditions.

Visuomotor Performance

In both CR and PLAC, visuomotor RT was impaired after the mentally fatiguing task compared with before, in both the simple (+42 ± 16 ms; $F_{1,\ 13} = 6.9$, $P = 0.021$, $\eta_p^2 = 0.347$) and the complex stimuli (+67 ± 28 ms; $F_{1,\ 13} = 5.9$, $P = 0.031$, $\eta_p^2 = 0.311$). No effect of the creatine supplementation was observed on visuomotor RT.

Perceptual and Physiological Parameters

Self-reported MF (assessed with the MFS) significantly changed throughout the protocol ($F_{11,\ 143} = 32.3$, $P < 0.001$, $\eta_p^2 = 0.713$; see Fig. 4A) in both CR and PLAC. Follow-up tests revealed that no change in MFS was present before the mentally fatiguing task. From pre- to posttrial, the mentally fatiguing task MFS did however increase from 17% ± 4% to 62% ± 7% ($P < 0.001$). After the mentally fatiguing task, MFS gradually decreased again to 45% ± 7% before commencement of the last strength endurance task, a level that was still significantly higher compared with before the mentally fatiguing task ($P = 0.029$). No difference in MFS between CR and PLAC was observed. Motivation (assessed with Moti; see Fig. 4B) to perform on the strength endurance ($P = 0.015$) and Flanker task ($P = 0.004$) was significantly lower after the mentally fatiguing task compared with before. This decrease in motivation in time was however not present for the visuomotor task performance. During the mentally fatiguing task motivation decreased gradually with prolonged performance (first task epoch = 64% ± 6%; eighth task epoch = 45% ± 7%; $P = 0.001$; see Fig. 4B). In addition, motivation was higher

TABLE 1. Dynamic handgrip strength endurance performance in the dominant and nondominant hand (lb).

	Dominant Hand													Nondominant Hand											
	1	2	3	4	5	6	7	8	9	10	11	12	% Change	1	2	3	4	5	6	7	8	9	10	11	12	% Change
CR—pretrial (handgrip strength ± SE), lb	98 ± 7	96 ± 7	89 ± 7	84 ± 6	88 ± 6	81 ± 6	81 ± 6	79 ± 6	76 ± 6	77 ± 6	71 ± 6	77 ± 6	79 ± 1	88 ± 7	83 ± 8	81 ± 7	77 ± 7	74 ± 6	73 ± 7	73 ± 8	73 ± 7	67 ± 7	70 ± 7	70 ± 6	71 ± 7	84 ± 2*
CR—posttrial (handgrip strength ± SE), lb	91 ± 8	90 ± 7	85 ± 7	84 ± 7	78 ± 7	79 ± 6	77 ± 7	75 ± 7	73 ± 7	75 ± 7	72 ± 7	74 ± 7	82 ± 2	84 ± 8	78 ± 7	78 ± 7	72 ± 7	70 ± 7	74 ± 7	72 ± 7	67 ± 7	66 ± 6	65 ± 7	64 ± 6	71 ± 7	84 ± 4*
PLAC—pretrial (handgrip strength ± SE), lb	98 ± 9	96 ± 7	94 ± 8	91 ± 7	87 ± 7	83 ± 8	83 ± 7	82 ± 7	76 ± 6	78 ± 6	80 ± 6	76 ± 6	83 ± 3	89 ± 8	87 ± 7	84 ± 7	79 ± 7	74 ± 8	73 ± 6	73 ± 6	71 ± 6	69 ± 6	68 ± 6	69 ± 5	68 ± 6	79 ± 1*
PLAC—posttrial (handgrip strength ± SE), lb	93 ± 8	89 ± 8	83 ± 9	85 ± 8	81 ± 7	81 ± 7	75 ± 9	75 ± 6	75 ± 6	78 ± 6	72 ± 6	77 ± 6	87 ± 4	88 ± 8	82 ± 8	80 ± 8	76 ± 7	73 ± 7	69 ± 6	69 ± 7	70 ± 7	68 ± 7	67 ± 6	66 ± 7	66 ± 7	80 ± 3*

Data are presented as mean ± SE.
*Significant main effect of condition ($P < 0.05$).

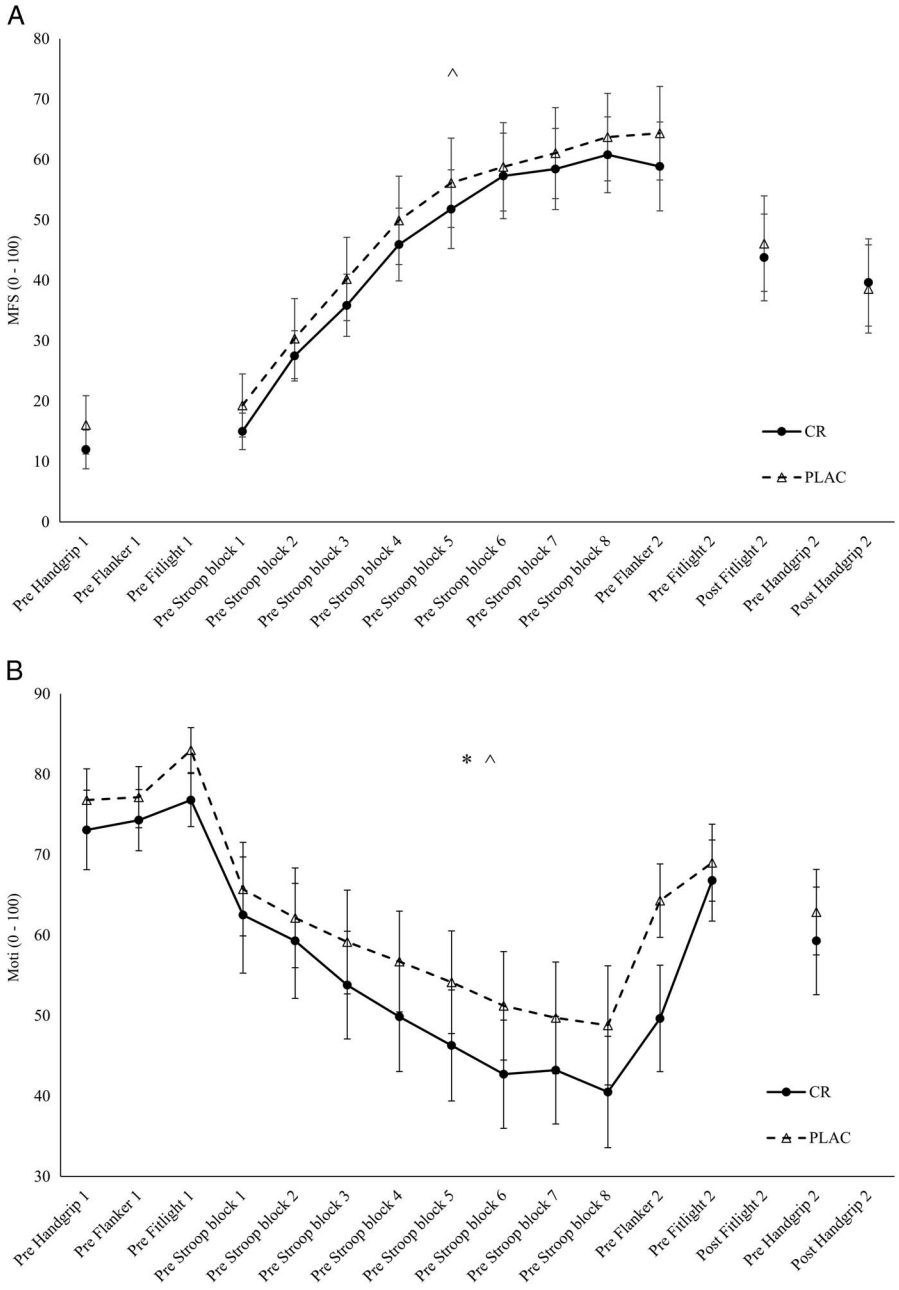

FIGURE 4—A, Self-reported MF throughout the protocol (0–100). ^Significant main effect of time ($P < 0.05$). Data are presented as mean ± SE. B, Self-reported motivation throughout the protocol (0–100). *Significant main effect of condition ($P < 0.05$). ^Significant main effect of time ($P < 0.05$). Data are presented as mean ± SE.

($F_{1, 13} = 8.9$, $P = 0.011$, $\eta_p^2 = 0.406$) in PLAC (63% ± 5%) compared with CR (57% ± 5%). Specifically, toward performance on the Stroop task, intrinsic and success motivation (assessed with the MMS) did not however differ between conditions. Besides a lower vigor in CR than that in PLAC before commencement of the Stroop task ($P = 0.027$), mood states did not differ between conditions before or after the Stroop task. In time, mood state did however differ; after the Stroop task, the fatigue ($P \leq 0.005$) and anger subscales ($P \leq 0.072$) increased compared with pretrial, whereas the vigor subscale decreased ($P \leq 0.013$). The Stroop task was not differently perceived between both conditions in any subscale of the NASA-TLX. Session RPE demonstrated that more exertion was perceived during the strength endurance task after the mentally fatiguing task compared with before (pretrial = 10.5 ± 0.6, posttrial = 11.4 ± 0.6; $F_{1, 13} = 10.4$, $P = 0.007$, $\eta_p^2 = 0.445$), this was not the case for perceived exertion during the visuomotor task.

HR ($F_{7, 70} = 23.6$, $P < 0.001$, $\eta_p^2 = 0.702$) and GLUC ($F_{1, 13} = 13.5$, $P = 0.003$, $\eta_p^2 = 0.509$) both dropped significantly before (HR = 83 ± 3 bpm, GLUC = 5.7 ± 0.2 mmol·L^{-1}) and after (HR = 71 ± 2 bpm; GLUC = 5.0 ± 0.1 mmol·L^{-1}) the mentally fatiguing task. No effect of condition was present.

DISCUSSION

The most important findings of the present study are as follows: 1) creatine supplementation improved physical (strength endurance) and prolonged cognitive (Stroop accuracy) performance; 2) MF-induced impairments in short sport-specific psychomotor and cognitive (Flanker) performance were not countered by creatine supplementation; and 3) creatine-induced physical and cognitive improvements are not explained by differences in the measured perceptual and/or physiological parameters.

Strength and Endurance

A handgrip task was included in the present study to evaluate the effect of MF on strength endurance. In addition, this task also enabled us to check whether the creatine supplementation was successful. Creatine supplementation is known to elevate muscle PCr stores and as such to positively affect muscle performance (28), mainly high-intensity muscle endurance (20). In the present study, this was confirmed; strength endurance was found to be improved in CR compared with PLAC in the nondominant hand. Muscle performance is of course also an important factor that underlies visuomotor performance (29). However, unlike handgrip strength endurance, visuomotor performance was not positively affected by creatine supplementation. This indicates that, although muscle performance was improved by creatine supplementation (e.g., strength endurance), this was not a limiting factor in visuomotor performance in the present study. A recent meta-analysis of Mielgo-Ayuso et al. (30) also concluded that soccer-specific agility performance is not improved by creatine supplementation. Other physical (e.g., neuromuscular) and cognitive (e.g., perceptual and decision making) components also known to play a role in agility (29) will most probably have determined visuomotor performance more decisively.

The improved strength endurance is interpreted as indirect evidence that the 7-d creatine supplementation protocol was successful in elevating PCr stores in the muscle (31). Whether this increase in muscle PCr stores also indicates brain PCr stores were successfully elevated is uncertain. On the basis of previous research, we might however assume so (13,32,33). Turner et al. (13,33) used magnetic resonance spectroscopy to demonstrate that a 7-d creatine supplementation (20 $g \cdot d^{-1}$) increases (+6% [13]; +9% [33]) brain creatine. The increase in brain PCr concentration, however, does seem to be smaller than what is commonly seen in skeletal muscle (about 10% vs about 20%) (32).

MF and Motivation

MF is a psychobiological state induced by prolonged exertion. It has been associated with multiple subjective, physiological, and behavioral alterations (see Van Cutsem et al. [1] for an overview). In both conditions, MF was equally present as is indicated by the elevated self-reported MF (+45% ± 6%) and decreased Flanker accuracy (−5% ± 2%) after the mentally fatiguing task in both CR and PLAC. This magnitude of change in self-reported MF by a 90-min Stroop task is comparable with the magnitude of change (i.e., +40% in the placebo trial [9]) that was observed in a previous study that also used a 90-min Stroop task (9). In both this study of Van Cutsem et al. (9) and the present study, this magnitude of change in self-reported MF was associated with a trend toward a drop in Stroop accuracy and a drop in Flanker accuracy (~5%). Furthermore, the slower visuomotor RT (simple stimuli, +42 ± 16 ms; complex stimuli, +67 ± 28 ms) and decreased strength endurance/RPE ratio (i.e., for a similar absolute strength endurance performance, more exertion was perceived) after completion of the MF task in both CR and PLAC are additional behavioral and perceptual alterations that substantiate equal MF was present in both conditions. A decrease in motivation is a possible mechanism through which MF might have triggered the above-mentioned perceptual and behavioral impairments in cognitive, strength endurance and visuomotor performance. In both conditions, participants were, according to the motivation VAS, less motivated to perform on the Flanker task and the strength endurance task after they performed the Stroop task compared with before. This finding conflicts with most of the previously performed research on MF and physical performance (22,34–38), where it is reported that the negative effect of MF on physical performance is not associated with a decrease in motivation to perform. Although motivation to physically perform is mostly unaffected by MF, it could still play a role (4,5). The present results justify this statement. MF impaired both cognitive and visuomotor performance, yet the motivational state decreased after the mentally fatiguing task only for cognitive performance. This indicates motivation plays a role but cannot completely account for the MF-induced performance impairments.

The finding that participants performed better on the Stroop task in CR compared with PLAC places the conclusion that MF was equally present in both conditions in question. Accuracy on the color stimuli (i.e., 75% of the stimuli) was higher in CR compared with PLAC (see Fig. 3). The statistical analysis revealed that this effect of creatine supplementation on Stroop accuracy was unaffected by time, indicating that the positive effect of creatine supplementation did not interact with the negative effect of MF. Visual interpretation of the Stroop accuracy data however nuances this interpretation (see Fig. 3). The significant difference between the average accuracy on the color stimuli in CR and PLAC clearly arises because of the differences in the later blocks of the Stroop task. Independently from this visual interpretation, the creatine-associated improvement in Stroop accuracy substantiates the previously shown cognition-enhancing effects of creatine supplementation (14,32) and indicates that creatine supplementation might be able to partially counteract the behavioral performance deterioration induced by MF.

A role for elevated brain PCr? To provide further insight into the improved Stroop performance after a 7-d creatine supplementation protocol, multiple parameters were assessed. Vigor before and motivation during the Stroop task were lower in CR compared with PLAC, whereas performance was observed to be improved in CR compared with PLAC (i.e., a paradoxical relation). No other mood states

(tension, depression, anger, and fatigue) differed between both conditions, and perceived workload (assessed with NASA-TLX) and MF (assessed with MFS) were also equal. Physiologically, both HR and GLUC changed to an equal extent during the Stroop task in both trials. As such, the perceptual and physiological parameters that were monitored do not seem to be involved in the creatine-induced increase in cognitive performance on the Stroop task. This confirms the findings of McMorris et al. (16) who also reported that creatine supplementation positively affected cognitive performance without any alteration in mood state at baseline and after 18, 24, and 36 h of sleep deprivation.

A potential role for the increase in brain creatine concentration (associated with the creatine supplementation) might be considered because the measured perceptual and physiological parameters are probably not involved in the creatine-induced improvement in Stroop performance. Previous research already showed that creatine supplementation possesses MF-counteracting properties (12,15,16). Watanabe et al. (12) suggested that these properties might be connected with creatine-associated alterations in brain energy metabolism (i.e., increased capacity of the PCr system). The current study further confirms the presence of the MF-counteracting properties of creatine supplementation (i.e., cognitive performance in the prolonged Stroop task improved after 7 d of supplementing creatine). Moreover, in the absence of any physiological or perceptual measure able to account for the effect of the creatine supplementation, a role for increased brain creatine concentration appears to be plausible and warrants further research.

Elevations of adenosine concentrations in specific brain regions (e.g., anterior cingulate cortex) have been suggested multiple times as a possible important moderator of the effect of MF on physical performance (5,39). Lovatt et al. (40) demonstrated that active spiking neurons release adenosine, leading to suppression of excitatory transmission. They proposed that this mechanism functions as a fatigue feedback signal to prevent metabolic exhaustion (e.g., a drop in PCr) under high-intensity activity (40). This is a possible pathway through which localized changes in physiological resources (e.g., a drop in PCr) could mediate neuronal excitability and cognitive performance as such, and this pathway might have been positively affected in the present study (i.e., increased brain PCr counteracted adenosine release).

Creatine Supplementation and Cognitive Function

Creatine supplementation has already been proposed to contain MF-counteracting properties (12,15,16). Moreover, McMorris et al. (16) suggested that creatine supplementation might only have a positive effect when the task is complex. The Stroop task is known to be a rather complex task, requiring response inhibition and sustained attention on controlled processes (24). The present study further complicated the task as it also placed demands on one's task-switching ability. The modified Stroop task worked with a general response rule and an exceptional response rule (see Methods), meaning that participants had to switch rules depending on specific color features of the stimuli. Because of the lower appearance probability of the meaning stimuli (25%) in comparison with the color stimuli (75%), a higher relative rate of switch trials was present in the meaning stimuli. As such, performance on the meaning stimuli relied more on task-switching ability, whereas performance on the color stimuli was a better measure of response inhibition. This suggests that creatine supplementation particularly improved response inhibition in the Stroop task.

This positive effect of creatine supplementation on response inhibition is however not reflected in performance on the visuomotor task or the Flanker task. In the study of Watanabe et al. (12), the MF-counteracting properties of creatine supplementation were evaluated with a prolonged cognitive task. Similarly as in our study, the positive effects of creatine supplementation on cognitive performance became most visible in the later stages of the task (i.e., the second half). This observation indicates that time on task may be an important factor for creatine supplementation to combat MF-associated performance decrements. Subsequently, this might explain why the MF-induced performance impairment on a short sport-specific psychomotor and cognitive task was not counteracted by creatine supplementation. Besides task duration, task complexity is another important factor that might possibly account for the differing effects of creatine supplementation on the Stroop task and the visuomotor and Flanker task. Like previously mentioned, McMorris et al. (16) already suggested that creatine supplementation might only have a positive effect when the task is complex. The Flanker task can be termed less complex than the Stroop task, as there was only one response rule during the Flanker task (i.e., indicate the direction of the target middle arrow), compared with two in the Stroop task. Moreover, only two answer options were present in the Flanker task, whereas four answer options were present in the Stroop task.

CONCLUSION

Creatine supplementation improved physical (strength endurance) and prolonged cognitive (Stroop accuracy) performance. However, it did not affect short sport-specific psychomotor or cognitive (Flanker) performance, nor did it affect the MF-associated impairment on these performances. Nonetheless, the improved prolonged cognitive (Stroop accuracy) performance indicates that creatine supplementation might be able to partially counteract the behavioral performance deterioration induced by MF. From a practical point of view, these results warrant further investigation in the potential role of creatine in countering the MF-associated decrements in prolonged (>7 min; e.g., 90-min soccer game) sport performance. From a mechanistic point of view, the results suggest a possible role of brain PCr in MF.

The authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. They thank the participants for their engagement in this study. They also thank the master thesis students Marius De Bruyn, Charlotte Vander Gracht, and Aline Verelst for their help with the data acquisition.

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