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Beyond Muscle: The Effects of Creatine Supplementation on Brain Creatine

The ergogenic and therapeutic effects of increasing muscle creatine by supplementation are well-recognized. It appears that similar benefits to brain function and cognitive processing may also be achieved with creatine supplementation, however research in this area is more limited, and important knowledge gaps remain. The purpose of this review is to provide a comprehensive overview of the current state of knowledge about the influence of creatine supplementation on brain function in healthy individuals. It appears that brain creatine is responsive to supplementation, however higher, or more prolonged dosing strategies than those typically used to increase muscle creatine, may be required to elicit an increase in brain creatine. The optimal dosing strategy to induce this response, is currently unknown, and there is an urgent need for studies investigating this. When considering the influence of supplementation strategies on cognitive processes, it appears that creatine is most likely to exert an influence in situations whereby cognitive processes are stressed, e.g. during sleep deprivation, experimental hypoxia, or during the performance of more complex, and thus more cognitively demanding tasks. Evidence exists indicating that increased brain creatine may be effective at reducing the severity of, or enhancing recovery from mild traumatic brain injury, however, only limited data in humans are available to verify this hypothesis, thus representing an exciting area for further research.

Keywords: Phosphorylcreatine; cerebral energy metabolism; dietary supplement; cognition; concussion

Highlights

- The brain is a highly metabolically active organ, and thus requires a constant energy supply. A high creatine content may theoretically enhance brain function, through facilitating rapid energy provision during times of accelerated ATP turnover.
- The brain does appear to be amenable to creatine supplementation. Optimal dosing protocols, particularly in healthy individuals, remain unknown although higher and/or more prolonged dosing protocols than those used to increase muscle creatine seem necessary.
- Creatine supplementation is most likely to positively impact cognitive processing during stressful situations, whereby brain creatine content is chronically or acutely suppressed.
- Preventive creatine supplementation may protect brain function in the event of acute stressors, such as sleep deprivation, acute hypoxia, exhaustive exercise or mTBI. Chronic reductions in brain creatine occur in a number of conditions. Therapeutic creatine supplementation restores brain creatine content, thus facilitating recovery of usual brain function.

Introduction

The effects of creatine monohydrate supplementation on muscle creatine levels and exercise performance in young adults have been well studied and extensively reviewed (reviewed in

Branch, 2003; Heaton et al., 2017; Rawson & Volek, 2003; Rawson, Miles, & Larson-Meyer, 2018). Further, the potential benefits of creatine monohydrate supplementation in older adults (reviewed in Candow, Chilibeck, & Forbes, 2014; Chilibeck, Kaviani, Candow, & Zello, 2017; Devries & Phillips, 2014; Gualano, Rawson, Candow, & Chilibeck, 2016; Rawson & Venezia, 2011), and patient populations (reviewed in Bender & Klopstock, 2016; Gualano, Roschel, Lancha, Brightbill, & Rawson, 2012) have also been thoroughly researched and well documented. The ingestion of about 20 g of creatine monohydrate per day (four 5 g servings) for about 5 days (or 3-5 g per day for about 30 days), first noted by Harris, Söderlund, and Hultman (1992) and Hultman, Söderlund, Timmons, Cederblad, and Greenhaff (1996), increases muscle creatine by about 20%. Larger increases in muscle creatine in response to creatine monohydrate ingestion can be obtained by combining the supplement with exercise, carbohydrate, or carbohydrate/protein combinations, although maximal creatine accumulation in mid-to-long-term (i.e. weeks to months) seems not to be affected by any of these factors (Hultman et al., 1996). Creatine's primary mechanistic role is to facilitate rapid energy provision during times of accelerated ATP degradation, which is achieved through transferring an *N*-phosphoryl group from phosphorylcreatine to ADP, a reaction which is reversibly catalysed by creatine kinase (CK). Additionally, the Cr-PCr system is proposed to act as a 'spatial energy buffer' whereby the different CK isoforms link the sites of ATP generation (i.e. the mitochondria), to sites of high ATP use (e.g. the sarcomere) (Greenhaff, 2001; Sahlin & Harris, 2011). Subsequently, creatine facilitates the maintenance of ATP homeostasis in tissues with high energy turnover, and supplementation has been shown to enhance performance of brief, high-intensity exercise, typically lasting less than 30 seconds, and resistance exercise performance (reviewed in Branch, 2003; Rawson & Volek, 2003).

As with muscle creatine, increasing brain creatine may confer benefits to athletes, non-athletes, older adults, and certain patient populations (reviewed in Gualano et al., 2012; Gualano et al., 2016; Rae & Broer, 2015; Rawson & Venezia, 2011). Relative to skeletal muscle, only a small percentage of total body creatine is in the brain (i.e. <5%) (Andres, Ducray, Schlattner, Wallimann, & Widmer, 2008). However, the brain is highly metabolically active, and, as in skeletal muscle, brain creatine is essential for energy production. This is corroborated by several lines of evidence, including: (i) the presence of CK isoforms in the central nervous system, (ii) the extensive mental disorders provoked by brain creatine depletion in creatine-deficient syndromes, and (iii) the partial reversal of these by creatine monohydrate supplementation (Kaldis, Hemmer, Zanolla, Holtzman, & Wallimann, 1996; Salomons et al., 2003; Stöckler et al., 1994). Indeed, the effects of creatine monohydrate supplementation on brain creatine and cognitive processing have become of interest to researchers and practitioners in a wide range of fields, from health to elite performance.

The influence of creatine supplementation on cognitive performance may occur due to a number of potential mechanisms. The brain is a highly metabolically active organ, responsible for 20% of basal metabolism, despite accounting for just 2% of body mass. The brain is therefore reliant on a constant energy supply in order to fulfil all functions, including maintenance of electrical membrane potentials, action potential propagation and PNS and CNS signalling (Gualano, Artioli, Poortmans, & Lancha Junior, 2010; Turner, Byblow, & Gant, 2015). During times of accelerated brain ATP turnover (as may be the case during the performance of complex cognitive tasks), or disrupted bioenergetic ATP turnover (as occurs during situations such as hypoxia,

sleep deprivation and various neurological conditions), creatine supplementation facilitates a more constant regeneration of ATP in the brain, thereby enhancing the ability to perform cognitive tasks. For example, Hammett, Wall, Edwards, and Smith (2010) reported a 16% reduction in Blood Oxygen Level Dependent (BOLD) amplitude after supplementing a group of young healthy adults with creatine. This attenuation of BOLD response was accompanied by an improved performance on various cognitive tests, and the authors hypothesized that their supplementation protocol likely increased cerebral phosphorylcreatine, thereby reducing metabolic demand and enhancing neural activity (Hammett et al., 2010). In support of this, Watanabe, Kato, and Kato (2002) used near-infrared spectroscopy to measure cerebral oxygenated and deoxygenated haemoglobin, and reported a reduction in oxygenated Hb, and elevation of deoxygenated Hb during the first part of a serial calculation task, along with a reduction in a mental fatigue index during the latter part of the cognitive test. Interestingly, however, Turner, Byblow, et al. (2015) reported that the magnitude of increase in brain creatine in their study did not predict the extent to which hypoxia-induced neurocognitive deficits were corrected in the creatine group. The authors suggested that the neuroprotective influence of creatine supplementation may occur, at least in part, due to non-energetic, and potential neuromodulatory mechanisms (Turner, Byblow, et al., 2015). Potential mechanisms through which this may be achieved include protecting against oxidative stress or mitochondrial membrane potential; Na^+/K^+-ATPase and/or CAMKII/CREB regulation (Souza et al., 2012). These mechanisms are as yet poorly understood, however, and further research is required to more fully investigate the potentially pleiotropic influence of creatine on brain function and cognitive processing.

The focus of this review is to describe the factors that affect brain creatine, including supplementation, and to determine if creatine monohydrate supplementation can improve cognitive processing or offer other benefits. It is important to identify that an ever-increasing body of evidence suggests the potential of creatine as a therapeutic agent in conditions whereby brain creatine is chronically suppressed, e.g. depression, schizophrenia, panic disorder, creatine deficiency syndromes caused by inborn errors of metabolism, and following a brain injury such as a concussion (reviewed in Allen, 2012; Kreider et al., 2017; Rae & Broer, 2015; Rawson et al., 2018; Rawson & Venezia, 2011), or to protect against the negative consequences of senescence (reviewed in Gualano et al., 2016). As these topics have been reviewed in detail elsewhere, the current review focuses on the use of creatine supplementation to enhance brain function in healthy individuals. The bulk of the research on safety and efficacy has been conducted on creatine monohydrate, and as other types of creatine supplements have not been as well studied, and so, unless otherwise specified, creatine supplementation will refer to creatine monohydrate supplementation in this article.

Factors influencing brain creatine: a brief overview

Creatine is a naturally occurring nutrient that is consumed in the diet, and synthesized in the liver, pancreas, and kidneys (Walker, 1979). Dietary creatine intake varies, but, in meat-eaters, is probably about 1-4 $g \cdot d^{-1}$. In foods, creatine is mostly localized to meat and fish at a concentration of about 3-5 $g \cdot kg^{-1}$ raw meat. Skeletal muscle, which contains about 95% of body creatine, cannot synthesize creatine, and so it is readily able to take up endogenously produced, supplemental, and/or dietary creatine. Unlike skeletal muscle, the brain can synthesize creatine,

and does not appear to rely on endogenous production from other organs (e.g. liver, pancreas, kidneys) or exogenous dietary sources (Braissant, Bachmann, & Henry, 2007). There is some indication that muscle creatine decreases with age, but this could also be a product of decreased physical activity, and not aging per se. It appears that muscle creatine does not increase with exercise training, but does decrease when research volunteers are placed on a vegetarian (i.e. low creatine) diet (Lukaszuk et al., 2002; Lukaszuk, Robertson, Arch, & Moyna, 2005). Brain creatine may also decrease with age (Laakso et al., 2003), but age-related decreases in brain creatine could also result from reduced brain activity or disease. In fact, it was recently shown that apparently healthy elderly and young individuals show comparable levels of brain phosphorylcreatine (Solis et al., 2017). Yazigi Solis et al. (2014) reduced muscle phosphorylcreatine in vegetarians, but no differences in brain phosphorylcreatine between vegetarians and omnivores, indicating that brain creatine is not influenced by habitual dietary creatine intake.

Effects of creatine supplementation on brain creatine

It is commonly accepted that a loading phase of 5 g (or ~0.3 $g \cdot kg^{-1}$) ingested 4 times daily for 5-7 days should increase muscle creatine and PCr by approximately 20-40%, while continued ingestion of 3-5 $g \cdot day^{-1}$ allows maintenance of these elevated creatine levels (Kreider et al., 2017). The dosing strategy required to optimally increase brain creatine levels has yet to be established, and this is largely due to a limited dataset that directly measures the influence of supplementation on brain creatine content. While direct measurement of muscle creatine and phosphorylcreatine can be accomplished through analysis of tissue obtained from muscle biopsies, assessment of brain creatine is more difficult. Direct measurement of brain creatine and phosphorylcreatine pre- and post-creatine supplementation can be accomplished in animals, but species differences in creatine uptake reveal the complications of generalizing data from this experimental model to humans (Ipsiroglu et al., 2001; Kreider, 2003; Nicastro et al., 2012; Tarnopolsky et al., 2003). Brain creatine can be assessed using proton or phosphorous nuclear magnetic resonance spectroscopy (H^1-NMR and P^{31}-NMR, respectively), but this is costly, not widely available, and, typically, labs can either measure total brain creatine (with H^1-NMR) or brain phosphorylcreatine (with P^{31}-NMR), but not both, due to time, funds, or technical constraints. These complications may have contributed to the fact that only a small number of human studies are available in which brain creatine levels were measured pre- and post-creatine supplementation. In addition, brain creatine content seems to be highly site-specific (reviewed by Rawson & Venezia, 2011), which renders it difficult to directly compare studies measuring creatine in different brain areas.

Table I describes the effects of creatine supplementation on brain creatine. As few studies are available in healthy individuals, we included reference to studies conducted in clinical populations. The available studies demonstrate that both brain creatine and phosphorylcreatine appear to increase in response to supplementation, although this appears to be a smaller increase than what is commonly seen in skeletal muscle (about 10% vs. about 20%). Several factors could explain the difference in tissue creatine uptake between muscle and brain. In the brain, there could be a compensatory response to creatine feeding in which brain creatine synthesis decreases and brain creatine normalizes despite supplementation. This is line with the emerging hypothesis that brain creatine, as compared to muscle, is less reliant on exogenous creatine ingestion

(Braissant et al., 2007; Merege-Filho et al., 2017; Solis et al., 2017; Yazigi Solis et al., 2014). In fact, the key enzymes involved in creatine biosynthesis (i.e. arginine:glycine amidinotransferase and *S*-adenosyl-l-methionine:*N*-guanidinoacetate methyltransferase) are present in astrocytes, neurons, and oligodendrocytes, therefore these cells are able to synthesize their own creatine (Andres et al., 2008; Braissant et al., 2007). On the other hand, the brain permeability to circulating creatine appears to be limited, likely due to the absence of creatine transporter expression in the astrocytes involved in the blood-brain barrier (Beard & Braissant, 2010).

Effects of creatine supplementation on brain creatine and phosphorylcreatine

Population	Supplementation protocol	Change in brain creatine	Reference
6 adults (2 M; 4 W) Age 26 yr	Single 20 g dose	↑ total creatine 3.1-7.7% (across different brain regions)	Dechent, et al. (1999)
6 adults (2 M; 4 W) Age 26 yr	20 $g \cdot d^{-1}$ for 28 d	↑ total creatine 4.7-14.6% (across different brain regions)	Dechent et al. (1999)
10 men (creatine group) Age 23 yr	0.3 $g \cdot kg^{-1} \cdot d^{-1}$ for 7 d; then 0.03 $g \cdot kg^{-1}$ d^{-1} for 7 d	↑ PCr 3.9%	Lyoo et al. (2003)
12 men (creatine group) Age 23 yr	20 $g \cdot d^{-1}$ for 5 d	No change	Wilkinson et al. (2006)
12 adults (7 M; 5 W) Age 32 yr	20 $g \cdot d^{-1}$ for 7 d	↑ creatine 5.2% ΔPCr −3.1 to 0% (across different brain regions)	Pan and Takahashi (2007)
5 female adolescents with MDD Age 13-18 yr	4 $g \cdot d^{-1}$ for 8 wk	↑ 6.4%	Kondo et al. (2011)
14 adult female amphetamine users with depression Age 37 yr	5 $g \cdot d^{-1}$ for 8 wk	↑ PCr 4.4%	Hellem et al. (2015)

15 adults (10 M; 5 W) Age 31 yr	20 $g \cdot d^{-1}$ for 7 d	↑ creatine 9.2%	Turner, Byblow, et al. (2015)
15 adults (10 M; 5 W) Age 31 yr	20 $g \cdot d^{-1}$ for 7 d	↑ creatine 5.9%	Turner, Russell, and Gant (2015)
22 adolescent females with SSRI-resistant MDD Age 17 yr	2 $g \cdot d^{-1}$ for 8 wk (n = 7) 4 $g \cdot d^{-1}$ for 8 wk (n = 8) 10 $g \cdot d^{-1}$ for 8 wk (n = 7)	↑ PCr 4.6% (2 g group) ↑ PCr 4.1% (4 g group) ↑ PCr 9.1% (10 g group)	Kondo et al. (2016)
35 children (creatine group) Age 11	0.3 $g \cdot kg^{-1}$ for 7 d	No effect	Merege-Filho et al. (2017)
15 children 16 adults 17 older adults (creatine groups) Age 11, 30, and 72 yr	0.3 $g \cdot kg^{-1} \cdot d^{-1}$ for 7 d	ΔPCr −0.7 to +3.9% (↑ muscle PCr +10.3 to 27.6%)	Solis et al. (2017)

PCr = phosphorylcreatine; SSRI = selective serotonin reuptake inhibitor; MDD = major depressive disorder.

This may explain how some studies report no increase, or even a decrease in brain creatine following supplementation, but this is still speculative. Only short-term data are available, so it is unknown if increased brain creatine resulting from supplementation can be maintained, as is the case with muscle creatine. If the brain is resistant to exogenous creatine, it would make sense that a higher dose, maintained for a longer period of time, as shown by Dechent et al. (1999), would be needed to increase and maintain elevated brain creatine levels. Several groups have demonstrated regional differences in both basal brain creatine and in the response to supplementation, highlighting that the ideal sampling area has not been determined. Finally, only one study is available that simultaneously assessed brain and muscle creatine, pre- and post-supplementation (Solis et al., 2017). In this investigation, brain phosphorylcreatine did not increase as a result of supplementation (range = −0.7 to +3.9), but muscle phosphorylcreatine increased (+10.3 to +27.6%) similarly to previous studies. This study ultimately suggests that the recommended dose of creatine effective to increase skeletal muscle creatine is not the same as the dose needed to increase brain creatine, with the latter remaining unknown. It does appear that larger and/or more sustained creatine doses may be required to elicit an increase in brain creatine content, and thus, identification of alternative dietary strategies to increase brain creatine content is of interest. Recently, guanidinoacetic acid (GAA, 3 $g \cdot day^{-1}$), a naturally occurring creatine precursor, was reported to have a superior influence on brain creatine content when compared to an equimolar dose of creatine (Ostojic, Ostojic, Drid, & Vranes, 2016), although it is important

to note that this finding was based on a preliminary investigation of just five participants. The safety and efficacy of GAA supplementation have yet to be ascertained, therefore, general consumption outside of a controlled research setting cannot currently be recommended. Finally, little can be concluded about the magnitude of changes in brain creatine/phosphorylcreatine in response to supplementation, since the vast majority of studies did not report individual data or the typical error of measurement (for the magnetic resonance spectroscopy (MRS) method), which precludes the determination of within- and between-subject variability and the rate of responsiveness to creatine supplementation, which is known for muscle creatine (~20-30% are non-responders; Greenhaff et al., 1993; Harris et al., 1992), but not for brain creatine.

Effects of creatine supplementation on cognitive processing

Research investigating the effect of creatine supplementation on cognitive performance in healthy humans is summarized in Table II. It is clear that creatine supplementation does have the potential to influence facets of brain function and cognitive processing in a number of models (Hammett et al., 2010; Ling et al., 2009; McMorris et al., 2006; McMorris, Harris, et al., 2007; Rae, Digney, McEwan, & Bates, 2003; Turner, Byblow, et al., 2015; Watanabe et al., 2002). However, wide variation in tests of cognitive function, dosing protocol, study populations and statistical approaches render it difficult to conclusively summarize and interpret the available evidence, meaning that only broad inferences can be made at this time. It seems that creatine is most likely to exert an influence in situations whereby cognitive processes are stressed, e.g. during sleep deprivation (McMorris et al., 2006; McMorris, Harris, et al., 2007), or experimental hypoxia (Turner, Byblow, et al., 2015). Additionally, it seems that more complex or demanding cognitive tests, such as central executive function, are more amenable to supplementation (McMorris et al., 2006; McMorris, Harris, et al., 2007) likely due to activation of larger brain areas with increased energy requirement and subsequently elevated requirement for ATP regeneration. There is, however, a lack of consistency in the cognitive test response to creatine supplementation, which makes it difficult to decipher the cognitive domains most susceptible to supplementation. For example, McMorris et al. (McMorris et al., 2006; McMorris, Harris, et al., 2007) conducted 2 complementary studies investigating the effect of creatine supplementation on cognitive function following 24 (McMorris et al., 2006) and 36 (McMorris, Harris, et al., 2007) hours of sleep deprivation. Both studies showed a positive effect of supplementation on at least one of the cognitive tests conducted, however different tests were impacted in each study. This was surprising, given that the same supplementation protocol and cognitive tests were used, while the study population were from a similar background (i.e. healthy young men and women). Another surprising finding from these studies, was that the study which used a longer period of sleep deprivation (24 vs. 36 hours), actually showed a lesser impact of creatine on cognitive function. One potential explanation for these differing results is the intensity of exercise employed in each study. Moderate intensity exercise was intermittently performed throughout the 36-hour sleep deprivation trial, while mild-intensity exercise was performed during the 24-hour trial. Non-exhaustive exercise, which does not induce dehydration, has previously been reported to have a positive influence on cognition (Tomporowski & Ellis, 1986), and it is possible that the moderate intensity exercise used within the latter design by McMorris, Harris, et al. (2007) actually acted to protect cognitive processes against the negative influence of sleep deprivation, thus ameliorating the concomitant influence of creatine supplementation. This is an important point for authors investigating the influence of creatine supplementation on cognitive

function in active individuals to consider, and the potentially confounding influence of exercise (which may, in fact, be positive or negative), should be appropriately controlled for within the study design.

The influence of creatine supplementation on cognitive performance in healthy humans

Author (date)	Population (n)	Study design	Supplement ($g \cdot day^{-1}$)	Cognitive tests	Primary outcomes
Alves et al. (2013)	Healthy older women. Placebo (22); Creatine (25).	Double blind, randomized, placebo-controlled, parallel group trial.	20 $g \cdot day^{-1}$ of creatine monohydrate divided into 4 equal daily doses for 5 days, followed by a single dose of 5 $g \cdot day^{-1}$ for the remainder of the trial (24 weeks).	Mini-mental state examination, stroop test, trail making test, digit span test, delay recall test and the short version of the geriatric depression scale.	Creatine supplementation did not influence cognitive performance.
Benton and Donohoe (2011)	Healthy female students, including vegan or vegetarians (70) and meat-eaters (51). Placebo (60); Creatine (61).	Double blind, randomized, placebo-controlled, parallel group trial.	20 $g \cdot day^{-1}$ of creatine monohydrate, divided into 4 equal daily doses for 5 days.	Word recall, simple and choice reaction time, rapid visual information processing and controlled oral word association test.	Word recall test performance was reduced in the meat-eating group following creatine supplementation ($p < .001$), and post-supplementation performance was higher in the vegetarians than in the meat-eaters ($p < .01$). The placebo group

					had more reaction time variability in the post-test, whereas the creatine group maintained performance pre-post on this parameter. No other cognitive variable was influenced by supplementation.
Cook, Crewther, Kilduff, Drawer, and Gaviglio (2011)	Professional rugby backs (10) who were sleep deprived (3-5 hours on the night preceding the test)	Blinded, randomized, placebo-controlled repeated-measures trial.	50 or 100 mg $kgBW^{-1}$ of creatine monohydrate for 1 day.	Repeated rugby passing skill task.	Sleep deprivation caused a significant reduction in passing accuracy, which was reversed by creatine supplementation. The larger dose (100 $mg \cdot kg^{-1}$) trended toward a greater effect on skill performance than 50 $mg \cdot kg^{-1}$.
Hammett et al. (2010)	Healthy young adults. Placebo	Placebo-controlled, parallel group trial.	20 $g \cdot day^{-1}$, divided into 2 equal daily doses for 5	Backward digit span test and ravens advanced progressive	Backward digit span performance was increased

	(11); Creatine (11).		days, followed by a single dose of 5 $g \cdot day^{-1}$ for 2 additional days.	matrices. BOLD response to visual stimuli was assessed my fMRI.	(26.9%) in the creatine supplement group ($p = .0069$). A non-significant increase in RAPM was also reported (9.6%, $p = .0745$). BOLD amplitude was reduced following creatine supplementation (16%, $p < .05$).
Ling, Kritikos, and Tiplady (2009)	Healthy young men (22) and women (12). Placebo (13); Creatine (13)	Double-blinded, placebo-controlled parallel group trial.	5 $g \cdot day^{-1}$ of creatine ethyl ester for 15 days.	Memory scanning, number-pair matching, sustained attention, arrow flankers and IQ test.	Some aspect of improvement was reported in all the cognitive tests performed in the creatine supplement group.
McMorris et al. (2006)	Healthy young men (17) and women (3) who were sleep deprived (24 hrs). Placebo (9); Creatine (10).	Double-blinded, placebo-controlled, parallel group trial.	20 $g \cdot day^{-1}$ of creatine monohydrate divided into 4 equal daily doses for 7 days.	Random number generation, forward and backward recall, visual reaction time, static balance and mood state (POMS).	After 24 hours, the extent of sleep deprivation induced performance reduction was attenuated in the creatine compared to the placebo

					group for random movement generation, choice reaction time, balance and mood.
McMorris, Mielcarz, Harris, Swain, and Howard (2007)	Healthy elderly men (16) and women (16). Placebo (15); Creatine (17).	Double-blinded, placebo-controlled, parallel group trial.	20 $g \cdot day^{-1}$ of creatine monohydrate divided into 4 equal daily doses for 7 days.	Random number generation, forward and backward recall, long-term memory tests (photo recall).	Forward number recall, forward and backward spatial recall and long-term memory (photo recall) performance were enhanced in the creatine supplementation group.
McMorris, Harris, et al. (2007)	Healthy young men (20) who were sleep deprived (36 hours). Placebo (9); Creatine (10).	Double-blinded, placebo-controlled, parallel group trial.	20 $g \cdot day^{-1}$ of creatine monohydrate divided into 4 equal daily doses for 7 days.	Random number generation, short-term number recall, visual reaction time, cognitive effort (NASA-TLX), dynamic balance test and mood state (POMS).	Performance on the random number generation test was improved following creatine supplementation.
Merege-Filho et al. (2017)	Healthy male and female children aged 10-12 years. Placebo (32);	Double blind, randomized, placebo-controlled, parallel group trial.	0.3 $g \cdot kg^{-1}$ divided into 4 equal doses for 7 days.	Stroop test, rey auditory learning test, raven progressive matrices and trail making test. Brain creatine in the prefrontal cortex,	Cognitive function and brain creatine levels were not influenced by creatine supplementation.

	Creatine (35).			left hippocampus and occipital lobe was measured in a randomly assigned subset of children (26).	
Rae and Broer (2015)	Vegan or vegetarian male and female healthy young adults (45).	Double-blinded, randomized, placebo-controlled, cross-over design.	5 $g \cdot day^{-1}$ of creatine monohydrate 6 weeks.	Ravens advanced progressive matrices, Wechsler auditory backward digit span task.	Creatine group improved performance on the RAPM test when completed under time pressure, and the backward digit span task.
Rawson et al. (2008)	Male (13) and female (9) young healthy adults.	Double-blinded, randomized, placebo-controlled parallel group trial.	0.03 $g \cdot kg^{-1}$ of creatine monohydrate for 6 weeks.	Automated neuropsychological assessment metrics (ANAM), which includes tests for simple reaction time, code substitution, logical reasoning, mathematical processing, running memory and memory recall.	Cognitive function was not affected by creatine supplementation.
Turner, Byblow, et al. (2015)	Healthy male (10) and female (5) young adults exposed to severe	Double-blinded, randomized, placebo-controlled cross-over trial.	20 $g \cdot day^{-1}$ of creatine monohydrate, divided into 4 equal daily doses for 7 days, with 5	Neuropsychological test battery comprising verbal and visual memory, finger tapping, symbol digit coding stroop test, test of	Brain creatine content was increased following supplementation. Creatine supplementation offset

	experimental hypoxia.		weeks washout between trials.	shifting attention, continuous performance test, alertness and peripheral and corticomotor excitability. Total neural Cr concentration was assessed by MRS.	hypoxia-induced decrements in a number of cognitive tests, particularly complex attention.
Watanabe et al. (2002)	Healthy male and female young adults. Placebo (12); Creatine (12).	Double-blinded, randomized placebo-controlled parallel group trial.	8 g·day^{-1} of creatine monohydrate divided into 8 equal doses for 5 days.	Serial calculation task (Uchida-Kraepelin test). Near-infrared spectroscopy was used to measure cerebral haemoglobin oxygenation and deoxygenation.	Both groups increased mean performance on the serial calculation task. Mental fatigue, assessed during the second half of the test using linear regression was increased in the creatine group only. The creatine supplementation group also showed lower oxygenated haemoglobin, and higher deoxygenated haemoglobin during the first half of the cognitive task.

The evidence supporting the use of creatine supplementation to enhance cognitive processing in unstressed, healthy individuals is contrasting, with a positive influence reported by some

(Hammett et al., 2010; Ling et al., 2009; Rae et al., 2003; Watanabe et al., 2002), but not others (Alves et al., 2013; Merege-Filho et al., 2017; Rawson et al., 2008). Some evidence exists suggesting that vegetarians may differentially respond to creatine supplementation when compared to meat-eaters. Rae et al. (2003) reported that cognitive performance was improved after a group of healthy, unstressed vegans and vegetarians supplemented with 5 $g \cdot day^{-1}$ of creatine monohydrate for 6 weeks, indicating that vegetarians may be more susceptible to the effects of creatine than meat-eaters, although a control group of meat-eaters would be required to confirm this. The hypothesis is however partially supported by Benton and Donohoe (2011) who reported that creatine supplementation resulted in a greater effect on memory in a group of vegetarians compared with meat-eaters. The results of this particular study should be interpreted with caution, as the vegetarian group did not actually improve performance following supplementation, and the reported post-supplementation difference was due to a reduction in performance in the meat-eaters. Nonetheless, collectively these two studies do appear to indicate a differential response between meat-eaters and vegetarians and it is plausible to hypothesize that non-meat-eaters, who have lower exogenous creatine intakes are more susceptible to the cognitive performance enhancing effects of creatine supplementation. This hypothesis is not however supported by the findings of Yazigi Solis et al. (2014), who reported similar brain creatine content in meat-eaters and vegetarians, and who concluded that brain creatine content relies on endogenous synthesis rather than dietary intake. Further research is therefore required to more fully investigate if meat-eaters and vegetarians do in fact have a different neurological response to creatine supplementation.

Whether or not potential cognitive improvements brought about through creatine supplementation can transfer to performance enhancements in the field is particularly relevant to athletes. This was investigated by Cook et al. (2011), who reported that sleep deprivation induced reductions in rugby throwing accuracy were attenuated by acute creatine supplementation (Cook et al., 2011). This study provides promising data of a potential enhancement of skilled motor performance under a stressful condition, in response to creatine supplementation. These results are not supported by other studies, however, which reported no impact of creatine supplementation on soccer passing accuracy (Cox, Mujika, Tumilty, & Burke, 2002; Hamid, Rahnama, Moghadasi, & Ranjbar, 2012). There are a number of potential explanations for this ambiguity in study findings. For example, the rugby passing test used by Cook et al. (2011) was time-constrained, while the soccer passing accuracy test was not, and is it plausible that the added pressure of time-constraint increased the cognitive demand required, thus rendering it more amenable to creatine supplementation. A more likely explanation, however, is that the rugby players participating in the study by Cook et al. (2011) were sleep deprived, adding weight to the hypothesis that creatine supplementation is most likely to exert its ergogenic effect when cognition is stressed. It is important to note that none of the studies investigating the effect of creatine supplementation on skilled motor performance provided data on brain creatine levels, and it is questionable whether the acute protocol used by Cook et al. (2011) would have resulted in increased brain creatine content, meaning that the mechanisms underpinning the improved performance reported in this study are uncertain.

Very few studies have simultaneously reported data related to the influence of creatine supplementation on brain creatine levels and cognitive function, making it difficult to ascertain whether the results attained are directly due to increased brain creatine levels. As discussed in the

previous section, it appears likely that the brain is capable of exogenously maintaining adequate brain creatine levels, and that either higher dosing protocols (Solis et al., 2017) or increased creatine requirement due to the influence of a stressor may be required in order to exert an influence. In support of this, Merege-Filho et al. (2017), recently investigated the influence of creatine supplementation (0.3 $g \cdot kg^{-1} \cdot day^{-1}$ creatine monohydrate for 7 days) on brain creatine levels and cognitive function in a group of healthy children aged 10-12 years, and reported no difference to either brain creatine content or cognitive function as a result of supplementation. The authors concluded that the lack of improvement to cognitive function may have been due to the lack of increase in brain creatine content, and indicated that creatine loading may only produce a functional effect on cognition under conditions of brain bioenergetic perturbation (Merege-Filho et al., 2017). Although most of the aforementioned studies investigating the influence of creatine supplementation on cognitive function did not directly investigate whether or not brain creatine levels increased, the data from these two studies (Merege-Filho et al., 2017; Solis et al., 2017) indicate that the lack of effect reported by many studies summarized in this review (Alves et al., 2013; Merege-Filho et al., 2017; Rawson et al., 2008) may be due, at least in part, to the inadequacy of the dosing strategy to increase brain creatine levels.

Mild traumatic brain injury: is there a protective role for brain creatine?

A nutritional intervention that might reduce severity of, or enhance recovery from, mild traumatic brain injury (mTBI), or concussion, would be highly valued in both the general and athletic populations. Following a mTBI there is a reduction in brain creatine (Vagnozzi et al., 2013) and a hypometabolic state. It is sensible that creatine supplementation, and subsequent increase in brain creatine, might offset these negative changes in energy status. Further, mTBI is characterized by numerous undesirable changes that could be lessened through creatine supplementation, including membrane disruption leading to calcium influx, nerve damage, mitochondrial dysfunction, oxidative stress, and inflammation (reviewed in Barrett, McBurney, & Ciappio, 2014; Dean, Arikan, Opitz, & Sterr, 2017). Few experimental data in humans are available, but two open-label creatine supplementation trials show improvements in cognition, communication, self-care, personality, and behaviour, and reductions in headaches, dizziness, and fatigue in children with TBI (Sakellaris et al., 2006; Sakellaris et al., 2008). Additionally, Turner and colleagues (Turner, Byblow, et al., 2015) showed increased brain creatine and cognitive processing during oxygen deprivation, a model that mimics the effects of mTBI. Although there are clearly species differences in response to creatine supplementation, animal data do indicate that creatine supplementation prior to TBI decreases damage by as much as 50% (Sullivan, Geiger, Mattson, & Scheff, 2000). Though few data available, and much more data are needed, the benefits of creatine supplementation could include reduced severity of, or enhanced recovery from, mTBI (reviewed in Kreider et al., 2017; Rawson et al., 2018).

Concluding remarks, perspectives and practical recommendations

Even though the role of creatine supplementation on brain functioning is promising, important scientific gaps remain that must be addressed (Box 1). First, bioavailability studies are necessary to show the optimal creatine supplementation protocol able to induce the greatest increases in brain creatine/phosphorylcreatine content. Evidence suggests that the blood-brain barrier is an obstacle for circulating creatine, which may require larger doses and/or longer protocols to

increase brain creatine as compared to muscle. In fact, the broad spectrum of creatine supplementation studies that span different dosing protocols (e.g. high-dose short-term, low dose longer-term), co-ingestion of other nutrients/compounds (e.g. carbohydrate, protein, insulin), different populations (e.g. vegetarians, elderly, patients, athletes) is unavailable for brain creatine adaptations. In addition, the sensitivity and reliability of NMR techniques used for measuring creatine/phosphorylcreatine in different areas of brain need to be determined, so that the precise magnitude of change in brain creatine, induced by creatine supplementation, can be ascertained at the individual level (Swinton, Hemingway, 2018). Studies combining the assessments of cognitive function and brain creatine levels are also relevant as they provide the ability to correlate changes in these two parameters, which in theory should occur in parallel. Ideally, therefore, creatine content should be assessed in specific brain areas involved in expected cognitive functions (e.g. measurement of brain creatine in hippocampus along with assessment of memory), allowing the mapping between brain creatine and cognitive processing in the context of supplementation.

Summary and Future directions

What is already known:
Creatine supplementation may increase brain creatine content, particularly in creatine-depleted conditions (e.g. creatine deficiencies).
Creatine supplementation may improve the performance in some cognitive tasks, particularly in stressful conditions (e.g. mental fatigue, exhaustive exercise).
What is unknown:
Can creatine supplementation increase brain creatine in healthy individuals?
If so: (a) To what extent? (b) In which brain region? (c) What is the ratio of responders: non-responders and which factors determine responsiveness? (d) What the ideal supplementation protocol?
Can creatine supplementation improve cognitive function in healthy individuals under non-stressful conditions?
Can creatine supplementation enhance recovery from, or reduce the severity of, mild traumatic brain injury?

The effects of creatine supplementation on brain function appear to be larger under stressful conditions that lead to acute (e.g. mental fatigue, exhaustive exercise) or chronic (e.g. aging, depression, post-traumatic stress disorder) depletion of brain creatine (see Figure 1), whereas no or minimal effect is shown in healthy individual under unstressed conditions. The exact circumstances and populations in which brain creatine is decreased should be determined as they are potential targets for creatine supplementation. Finally, although there appears to be a sound mechanistic basis for creatine supplementation to reduce severity of or enhance recovery from mTBI, which is supported by the animal data available, few data are available that demonstrate a protective effect in humans. If an athlete already ingests creatine supplements for a different reason (e.g. sport performance), and mTBI brain injury is a possibility in their sport, ingesting creatine may offer them brain benefits as well. Additionally, creatine supplements are widely available, inexpensive, and have a very good safety profile (Gualano et al., 2011, 2012; Hayashi et al., 2014; Lugaresi et al., 2013; Pereira et al., 2015; Persky & Rawson, 2007; Rawson, Clarkson, & Tarnopolsky, 2017), which also favours the decision to recommend creatine supplementation to athletes at higher risks of mTBI. Creatine may also be considered for other stressful situations whereby acute creatine reductions are likely to occur. As described above, creatine may offset the negative cognitive effects of sleep deprivation. There are a number of situations where this may be particularly relevant, and thus where creatine supplementation may be particularly efficacious. For example, athletes competing in multi-day tournaments have high requirements to maintain optimal cognitive functioning, however, sleep deprivation due to travel requirements, unfamiliar surroundings and intensive schedules is likely. In these situations, cognitive function may be enhanced or maintained through supplementation. Similarly, sleep deprivation and anxiety are common among students during exam periods, a time when optimal cognitive processing is essential. Finally, many cognitively demanding occupations require individuals to work over-night shifts and/or very long hours, e.g. medical personnel or pilots frequently work very long or unusual hours, and thus to have disrupted sleep patterns, however they may also be required to make important and at times vital decisions, and thus to require optimal cognitive processing. Individuals who are required to make important decisions under potentially stressful situations, particularly those characterized by disrupted sleep patterns, may therefore, benefit from the cognitive enhancing properties of creatine supplementation.

PHOTO (COLOR): Figure 1. Situations where creatine supplementation may enhance brain function. Panel A: Acute stressors, e.g. sleep deprivation, exhaustive exercise, acute hypoxia, cognitively demanding tasks or mTBI can cause a reduction in brain creatine, thus impacting brain function. Preventive supplementation creates a 'reserve' of brain creatine, protecting against the reduction caused by anticipated acute stressors, facilitating maintenance of usual brain function. Panel B: Some conditions are associated with chronically reduced brain creatine, e.g. cerebral creatine deficiency syndromes, depression, schizophrenia or senescence. Therapeutic creatine supplementation restores brain creatine content, facilitating recovery of usual brain function.

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References

1 Allen, P. J. (2012). Creatine metabolism and psychiatric disorders: Does creatine supplementation have therapeutic value? Neuroscience & Biobehavioral Reviews, 36 (5), 1442 - 1462. doi: 10.1016/j.neubiorev.2012.03.005

2 Alves, C. R., Merege Filho, C. A., Benatti, F. B., Brucki, S., Pereira, R. M., de Sa Pinto, A. L., ... Gualano, B. (2013). Creatine supplementation associated or not with strength training upon emotional and cognitive measures in older women: A randomized double-blind study. PLoS One, 8 (10), e76301. doi: 10.1371/journal.pone.0076301

3 Andres, R. H., Ducray, A. D., Schlattner, U., Wallimann, T., & Widmer, H. R. (2008). Functions and effects of creatine in the central nervous system. Brain Research Bulletin, 76 (4), 329 - 343. doi: 10.1016/j.brainresbull.2008.02.035

4 Barrett, E. C., McBurney, M. I., & Ciappio, E. D. (2014). Omega-3 fatty acid supplementation as a potential therapeutic aid for the recovery from mild traumatic brain injury/concussion. Advances in Nutrition, 5 (3), 268 - 277. doi: 10.3945/an.113.005280

5 Beard, E., & Braissant, O. (2010). Synthesis and transport of creatine in the CNS: Importance for cerebral functions. Journal of Neurochemistry, 115 (2), 297 - 313. doi: 10.1111/j.1471-4159.2010.06935.x

6 Bender, A., & Klopstock, T. (2016). Creatine for neuroprotection in neurodegenerative disease: End of story? Amino Acids, 48 (8), 1929 - 1940. doi: 10.1007/s00726-015-2165-0

7 Benton, D., & Donohoe, R. (2011). The influence of creatine supplementation on the cognitive functioning of vegetarians and omnivores. British Journal of Nutrition, 105 (7), 1100 - 1105. doi: 10.1017/S0007114510004733

8 Braissant, O., Bachmann, C., & Henry, H. (2007). Expression and function of AGAT, GAMT and CT1 in the mammalian brain. Subcellular Biochemistry, 46, 67 - 81. doi: 10.1007/978-1-4020-6486-9_4

9 Branch, J. D. (2003). Effect of creatine supplementation on body composition and performance: A meta-analysis. International Journal of Sport Nutrition and Exercise Metabolism, 13 (2), 198 - 226. doi: 10.1123/ijsnem.13.2.198

Candow, D. G., Chilibeck, P. D., & Forbes, S. C. (2014). Creatine supplementation and aging musculoskeletal health. Endocrine, 45 (3), 354 - 361. doi: 10.1007/s12020-013-0070-4

Chilibeck, P. D., Kaviani, M., Candow, D. G., & Zello, G. A. (2017). Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: A meta-analysis. Open Access Journal of Sports Medicine, 8, 213 - 226. doi: 10.2147/OAJSM.S123529

Cook, C. J., Crewther, B. T., Kilduff, L. P., Drawer, S., & Gaviglio, C. M. (2011). Skill execution and sleep deprivation: Effects of acute caffeine or creatine supplementation - A randomized placebo-controlled trial. Journal of the International Society of Sports Nutrition, 8, 2. doi: 10.1186/1550-2783-8-2

Cox, G., Mujika, I., Tumilty, D., & Burke, L. (2002). Acute creatine supplementation and performance during a field test simulating match play in elite female soccer players. International Journal of Sport Nutrition and Exercise Metabolism, 12 (1), 33 - 46. doi: 10.1123/ijsnem.12.1.33

Dean, P. J. A., Arikan, G., Opitz, B., & Sterr, A. (2017). Potential for use of creatine supplementation following mild traumatic brain injury. Concussion, 2 (2), CNC34. doi. 10.2217/cnc-2016-0016

Dechent, P., Pouwels, P. J., Wilken, B., Hanefeld, F., & Frahm, J. (1999). Increase of total creatine in human brain after oral supplementation of creatine-monohydrate. American Journal of Physiology, 277 (3 Pt 2), R698 - R704.

Devries, M. C., & Phillips, S. M. (2014). Creatine supplementation during resistance training in older adults—A meta-analysis. Medicine & Science in Sports & Exercise, 46 (6), 1194 - 1203. doi: 10.1249/MSS.0000000000000220

Greenhaff, P. L. (2001). The creatine-phosphocreatine system: There's more than one song in its repertoire. The Journal of Physiology, 537 (Pt 3), 657. doi: 10.1113/jphysiol.2001.013478

Greenhaff, P. L., Casey, A., Short, A. H., Harris, R., Söderlund, K., & Hultman, E. (1993). Influence of oral creatine supplementation of muscle torque during repeated bouts of maximal voluntary exercise in man. Clinical Science, 84 (5), 565 - 571. doi: 10.1042/cs0840565

Gualano, B., Artioli, G. G., Poortmans, J. R., & Lancha Junior, A. H. (2010). Exploring the therapeutic role of creatine supplementation. Amino Acids, 38 (1), 31 - 44. doi: 10.1007/s00726-009-0263-6

Gualano, B., de Salles Painelli, V., Roschel, H., Lugaresi, R., Dorea, E., Artioli, G. G., ... Lancha Junior, A. H. (2011). Creatine supplementation does not impair kidney function in type 2 diabetic patients: A randomized, double-blind, placebo-controlled, clinical trial. European Journal of Applied Physiology, 111 (5), 749 - 756. doi: 10.1007/s00421-010-1676-3

Gualano, B., Rawson, E. S., Candow, D. G., & Chilibeck, P. D. (2016). Creatine supplementation in the aging population: Effects on skeletal muscle, bone and brain. Amino Acids, 48 (8), 1793 - 1805. doi: 10.1007/s00726-016-2239-7

Gualano, B., Roschel, H., Lancha, A. H., Jr., Brightbill, C. E., & Rawson, E. S. (2012). In sickness and in health: The widespread application of creatine supplementation. Amino Acids, 43 (2), 519 - 529. doi: 10.1007/s00726-011-1132-7

Hamid, M., Rahnama, N., Moghadasi, M., & Ranjbar, K. (2012). Effect of creatine supplementation on sprint and skill performance in young soccer players. Middle East Journal of Scientific Research, 12 (3), 397 - 401. doi: 10.5829/idosi.mejsr.2012.12.3.64214

Hammett, S. T., Wall, M. B., Edwards, T. C., & Smith, A. T. (2010). Dietary supplementation of creatine monohydrate reduces the human fMRI BOLD signal. Neuroscience Letters, 479 (3), 201 - 205. doi: 10.1016/j.neulet.2010.05.054

Harris, R. C., Söderlund, K., & Hultman, E. (1992). Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. Clinical Science, 83 (3), 367 - 374. doi: 10.1042/cs0830367

Hayashi, A. P., Solis, M. Y., Sapienza, M. T., Otaduy, M. C., de Sa Pinto, A. L., Silva, C. A., ... Gualano, B. (2014). Efficacy and safety of creatine supplementation in childhood-onset systemic lupus erythematosus: A randomized, double-blind, placebo-controlled, crossover trial. Lupus, 23 (14), 1500 - 1511. doi: 10.1177/0961203314546017

Heaton, L. E., Davis, J. K., Rawson, E. S., Nuccio, R. P., Witard, O. C., Stein, K. W., ... Baker, L. B. (2017). Selected in-season nutritional strategies to enhance recovery for team sport athletes: A practical overview. Sports Medicine, 47 (11), 2201 - 2218. doi: 10.1007/s40279-017-0759-2

Hellem, T. L., Sung, Y. H., Shi, X. F., Pett, M. A., Latendresse, G., Morgan, J., ... Renshaw, P. F. (2015). Creatine as a novel treatment for depression in females using methamphetamine: A pilot study. Journal of Dual Diagnosis, 11 (3-4), 189 - 202. doi: 10.1080/15504263.2015.1100471

Hultman, E., Söderlund, K., Timmons, J. A., Cederblad, G., & Greenhaff, P. L. (1996). Muscle creatine loading in men. Journal of Applied Physiology, 81 (1), 232 - 237. doi: 10.1152/jappl.1996.81.1.232

Ipsiroglu, O. S., Stromberger, C., Ilas, J., Hoger, H., Muhl, A., & Stockler-Ipsiroglu, S. (2001). Changes of tissue creatine concentrations upon oral supplementation of creatine-monohydrate in various animal species. Life Sciences, 69 (15), 1805 - 1815. doi: 10.1016/S0024-3205(01)01268-1

Kaldis, P., Hemmer, W., Zanolla, E., Holtzman, D., & Wallimann, T. (1996). 'Hot spots' of creatine kinase localization in brain: Cerebellum, hippocampus and choroid plexus. Developmental Neuroscience, 18 (5-6), 542 - 554. doi: 10.1159/000111452

Kondo, D. G., Forrest, L. N., Shi, X., Sung, Y. H., Hellem, T. L., Huber, R. S., & Renshaw, P. F. (2016). Creatine target engagement with brain bioenergetics: A dose-ranging phosphorus-31

magnetic resonance spectroscopy study of adolescent females with SSRI-resistant depression. Amino Acids, 48 (8), 1941 - 1954. doi: 10.1007/s00726-016-2194-3

Kondo, D. G., Sung, Y. H., Hellem, T. L., Fiedler, K. K., Shi, X., Jeong, E. K., & Renshaw, P. F. (2011). Open-label adjunctive creatine for female adolescents with SSRI-resistant major depressive disorder: A 31-phosphorus magnetic resonance spectroscopy study. Journal of Affective Disorders, 135 (1-3), 354 - 361. doi: 10.1016/j.jad.2011.07.010

Kreider, R. B. (2003). Species-specific responses to creatine supplementation. American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 285 (4), R725 - R726. doi: 10.1152/ajpregu.00375.2003

Kreider, R. B., Kalman, D. S., Antonio, J., Ziegenfuss, T. N., Wildman, R., Collins, R., ... Lopez, H. L. (2017). International society of sports nutrition position stand: Safety and efficacy of creatine supplementation in exercise, sport, and medicine. Journal of the International Society of Sports Nutrition, 14, 273. doi: 10.1186/s12970-017-0173-z

Laakso, M. P., Hiltunen, Y., Kononen, M., Kivipelto, M., Koivisto, A., Hallikainen, M., & Soininen, H. (2003). Decreased brain creatine levels in elderly apolipoprotein E epsilon 4 carriers. Journal of Neural Transmission, 110 (3), 267 - 275. doi: 10.1007/s00702-002-0783-7

Ling, J., Kritikos, M., & Tiplady, B. (2009). Cognitive effects of creatine ethyl ester supplementation. Behavioural Pharmacology, 20 (8), 673 - 679. doi: 10.1097/FBP.0b013e3283323c2a

Lugaresi, R., Leme, M., de Salles Painelli, V., Murai, I. H., Roschel, H., Sapienza, M. T., ... Gualano, B. (2013). Does long-term creatine supplementation impair kidney function in resistance-trained individuals consuming a high-protein diet? Journal of the International Society of Sports Nutrition, 10 (1), 26. doi: 10.1186/1550-2783-10-26

Lukaszuk, J. M., Robertson, R. J., Arch, J. E., Moore, G. E., Yaw, K. M., Kelley, D. E., ... Moyna, N. M. (2002). Effect of creatine supplementation and a lacto-ovo-vegetarian diet on muscle creatine concentration. International Journal of Sport Nutrition and Exercise Metabolism, 12 (3), 336 - 348. doi: 10.1123/ijsnem.12.3.336

Lukaszuk, J. M., Robertson, R. J., Arch, J. E., & Moyna, N. M. (2005). Effect of a defined lacto-ovo-vegetarian diet and oral creatine monohydrate supplementation on plasma creatine concentration. The Journal of Strength and Conditioning Research, 19 (4), 735 - 740. doi: 10.1519/R-16224.1

Lyoo, I. K., Kong, S. W., Sung, S. M., Hirashima, F., Parow, A., Hennen, J., ... Renshaw, P. F. (2003). Multinuclear magnetic resonance spectroscopy of high-energy phosphate metabolites in human brain following oral supplementation of creatine-monohydrate. Psychiatry Research: Neuroimaging, 123 (2), 87 - 100. doi: 10.1016/S0925-4927(03)00046-5

McMorris, T., Harris, R. C., Howard, A. N., Langridge, G., Hall, B., Corbett, J., ... Hodgson, C. (2007). Creatine supplementation, sleep deprivation, cortisol, melatonin and behavior. Physiology & Behavior, 90 (1), 21 - 28. doi: 10.1016/j.physbeh.2006.08.024

McMorris, T., Harris, R. C., Swain, J., Corbett, J., Collard, K., Dyson, R. J., ... Draper, N. (2006). Effect of creatine supplementation and sleep deprivation, with mild exercise, on cognitive and psychomotor performance, mood state, and plasma concentrations of catecholamines and cortisol. Psychopharmacology, 185 (1), 93 - 103. doi: 10.1007/s00213-005-0269-z

McMorris, T., Mielcarz, G., Harris, R. C., Swain, J. P., & Howard, A. (2007). Creatine supplementation and cognitive performance in elderly individuals. Neuropsychology, Development and Cognition. Seciton B, Aging, Neuropsychology and Cognition, 14 (5), 517 - 528. doi: 10.1080/13825580600788100

Merege-Filho, C. A., Otaduy, M. C., de Sa-Pinto, A. L., de Oliveira, M. O., de Souza Goncalves, L., Hayashi, A. P., ... Gualano, B. (2017). Does brain creatine content rely on exogenous creatine in healthy youth? A proof-of-principle study. Applied Physiology, Nutrition, and Metabolism, 42 (2), 128 - 134. doi: 10.1139/apnm-2016-0406

Nicastro, H., Gualano, B., de Moraes, W. M., de Salles Painelli, V., da Luz, C. R., dos Santos Costa, A., ... Lancha, A. H., Jr. (2012). Effects of creatine supplementation on muscle wasting and glucose homeostasis in rats treated with dexamethasone. Amino Acids, 42 (5), 1695 - 1701. doi: 10.1007/s00726-011-0871-9

Ostojic, S. M., Ostojic, J., Drid, P., & Vranes, M. (2016). Guanidinoacetic acid versus creatine for improved brain and muscle creatine levels: A superiority pilot trial in healthy men. Applied Physiology, Nutrition, and Metabolism, 41 (9), 1005 - 1007. doi: 10.1139/apnm-2016-0178

Pan, J. W., & Takahashi, K. (2007). Cerebral energetic effects of creatine supplementation in humans. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 292 (4), R1745 - R1750. doi: 10.1152/ajpregu.00717.2006

Pereira, R. T., Dorr, F. A., Pinto, E., Solis, M. Y., Artioli, G. G., Fernandes, A. L., ... Gualano, B. (2015). Can creatine supplementation form carcinogenic heterocyclic amines in humans? The Journal of Physiology, 593 (17), 3959 - 3971. doi: 10.1113/JP270861

Persky, A. M., & Rawson, E. S. (2007). Safety of creatine supplementation. Subcellular Biochemistry, 46, 275 - 289. doi: 10.1007/978-1-4020-6486-9_14

Rae, C. D., & Broer, S. (2015). Creatine as a booster for human brain function. How might it work? Neurochemistry International, 89, 249 - 259. doi: 10.1016/j.neuint.2015.08.010

Rae, C. D., Digney, A. L., McEwan, S. R., & Bates, T. C. (2003). Oral creatine monohydrate supplementation improves brain performance: A double-blind, placebo-controlled, cross-over trial. Proceedings of the Royal Society B: Biological Sciences, 270 (1529), 2147 - 2150. doi: 10.1098/rspb.2003.2492

Rawson, E. S., Clarkson, P. M., & Tarnopolsky, M. A. (2017). Perspectives on exertional rhabdomyolysis. Sports Medicine, 47 (Suppl 1), 33 - 49. doi: 10.1007/s40279-017-0689-z

Rawson, E. S., Lieberman, H. R., Walsh, T. M., Zuber, S. M., Harhart, J. M., & Matthews, T. C. (2008). Creatine supplementation does not improve cognitive function in young adults. Physiology & Behavior, 95 (1-2), 130 - 134. doi: 10.1016/j.physbeh.2008.05.009

Rawson, E. S., Miles, M. P., & Larson-Meyer, D. E. (2018). Dietary supplements for health, adaptation, and recovery in athletes. International Journal of Sport Nutrition and Exercise Metabolism, 28, 188 - 199. doi: 10.1123/ijsnem.2017-0340

Rawson, E. S., & Venezia, A. C. (2011). Use of creatine in the elderly and evidence for effects on cognitive function in young and old. Amino Acids, 40 (5), 1349 - 1362. doi: 10.1007/s00726-011-0855-9

Rawson, E. S., & Volek, J. S. (2003). Effects of creatine supplementation and resistance training on muscle strength and weightlifting performance. The Journal of Strength and Conditioning Research, 17 (4), 822 - 831.

Sahlin, K., & Harris, R. C. (2011). The creatine kinase reaction: A simple reaction with functional complexity. Amino Acids, 40 (5), 1363 - 1367. doi: 10.1007/s00726-011-0856-8

Sakellaris, G., Kotsiou, M., Tamiolaki, M., Kalostos, G., Tsapaki, E., Spanaki, M., ... Evangeliou, A. (2006). Prevention of complications related to traumatic brain injury in children and adolescents with creatine administration: An open label randomized pilot study. The Journal of Trauma: Injury, Infection, and Critical Care, 61 (2), 322 - 329. doi: 10.1097/01.ta.0000230269.46108.d5

Sakellaris, G., Nasis, G., Kotsiou, M., Tamiolaki, M., Charissis, G., & Evangeliou, A. (2008). Prevention of traumatic headache, dizziness and fatigue with creatine administration. A pilot study. Acta Paediatrica, 97 (1), 31 - 34. doi: 10.1111/j.1651-2227.2007.00529.x

Salomons, G. S., van Dooren, S. J., Verhoeven, N. M., Marsden, D., Schwartz, C., Cecil, K. M., ... Jakobs, C. (2003). X-linked creatine transporter defect: An overview. Journal of Inherited Metabolic Disease, 26 (2-3), 309 - 318. doi: 10.1023/A:1024405821638

Solis, M. Y., Artioli, G. G., Otaduy, M. C. G., Leite, C. D. C., Arruda, W., Veiga, R. R., & Gualano, B. (2017). Effect of age, diet and tissue type on PCr response to creatine supplementation. Journal of Applied Physiology, 123, 407 - 414. doi: 10.1152/japplphysiol.00248.2017

Souza, M. A., Magni, D. V., Guerra, G. P., Oliveira, M. S., Furian, A. F., Pereira, L., ... Royes, L. F. (2012). Involvement of hippocampal CAMKII/CREB signaling in the spatial memory retention induced by creatine. Amino Acids, 43 (6), 2491 - 2503. doi: 10.1007/s00726-012-1329-4

Stöckler, S., Holzbach, U., Hanefeld, F., Marquardt, I., Helms, G., Requart, M., ... Frahm, J. (1994). Creatine deficiency in the brain: A new, treatable inborn error of metabolism. Pediatric Research, 36 (3), 409 - 413. doi: 10.1203/00006450-199409000-00023

Sullivan, P. G., Geiger, J. D., Mattson, M. P., & Scheff, S. W. (2000). Dietary supplement creatine protects against traumatic brain injury. Annals of Neurology, 48 (5), 723 - 729. doi: 10.1002/1531-8249(200011)48:5<723::AID-ANA5>3.0.CO;2-W

Swinton, P., Hemingway, B. S., Saunders, B., Gualano, B., & Dolan, E. (2018). A statistical framework to interpret individual response to intervention: Paving the way for personalized nutrition and exercise prescription. Frontiers in Nutrition, 5, 41 -. doi: 10.3389/fnut.2018.00041

Tarnopolsky, M. A., Bourgeois, J. M., Snow, R., Keys, S., Roy, B. D., Kwiecien, J. M., & Turnbull, J. (2003). Histological assessment of intermediate- and long-term creatine monohydrate supplementation in mice and rats. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 285 (4), R762 - R769. doi: 10.1152/ajpregu.00270.2003

Tomporowski, P. D., & Ellis, N. R. (1986). Effects of exercise on cognitive processes: A review. Psychological Bulletin, 99 (3), 338 - 346. doi: 10.1037/0033-2909.99.3.338

Turner, C. E., Byblow, W. D., & Gant, N. (2015). Creatine supplementation enhances corticomotor excitability and cognitive performance during oxygen deprivation. Journal of Neuroscience, 35 (4), 1773 - 1780. doi: 10.1523/JNEUROSCI.3113-14.2015

Turner, C. E., Russell, B. R., & Gant, N. (2015). Comparative quantification of dietary supplemented neural creatine concentrations with (1)H-MRS peak fitting and basis spectrum methods. Magnetic Resonance Imaging, 33 (9), 1163 - 1167. doi: 10.1016/j.mri.2015.06.018

Vagnozzi, R., Signoretti, S., Floris, R., Marziali, S., Manara, M., Amorini, A. M., ... Tavazzi, B. (2013). Decrease in N-acetylaspartate following concussion may be coupled to decrease in creatine. Journal of Head Trauma Rehabilitation, 28 (4), 284 - 292. doi: 10.1097/HTR.0b013e3182795045

Walker, J. B. (1979). Creatine: Biosynthesis, regulation, and function. Advances in Enzymology and Related Areas of Molecular Biology, 50, 177 - 242.

Watanabe, A., Kato, N., & Kato, T. (2002). Effects of creatine on mental fatigue and cerebral hemoglobin oxygenation. Neuroscience Research, 42 (4), 279 - 285. doi: 10.1016/S0168-0102(02)00007-X

Wilkinson, I. D., Mitchel, N., Breivik, S., Greenwood, P., Griffiths, P. D., Winter, E. M., & Van Beek, E. J. (2006). Effects of creatine supplementation on cerebral white matter in competitive sportsmen. Clinical Journal of Sport Medicine, 16 (1), 63 - 67. doi: 10.1097/01.jsm.0000176372.67398.c8

Yazigi Solis, M., de Salles Painelli, V., Giannini Artioli, G., Roschel, H., Concepcion Otaduy, M., & Gualano, B. (2014). Brain creatine depletion in vegetarians? A cross-sectional (1)H-magnetic resonance spectroscopy ((1)H-MRS) study. British Journal of Nutrition, 111 (7), 1272 - 1274. doi: 10.1017/S0007114513003802

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