Mini-Review

Creatine Supplementation: More Is Likely Better for Brain Bioenergetics, Health and Function

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ABSTRACT

Creatine monohydrate (CrM) is one of the most well-researched and effective ergogenic supplements. Given the constant energy supply required by the brain, there has been a paradigm shift from CrM for skeletal muscle benefits to potentially improving brain bioenergetics, health and function. Accumulating research indicates that CrM is capable of increasing brain creatine stores which may help explain improvements in cognitive functioning particularly during times of metabolic stress (i.e., sleep deprivation, hypoxia, mental fatigue, and traumatic brain injury [TBI]). Due to the attenuation of creatine transport kinetics and the blood-brain barrier (BBB), speculation exists that higher doses of CrM are needed to optimize brain creatine levels. However, optimal CrM doses are currently unknown. Beyond these key variables, strategies such as glycocyamine supplementation (natural precursor to creatine), cyclocreatine supplementation (creatine analog), intranasal administration, and creatine transporter (CT1) modulation appear promising for increasing total and regional brain creatine levels which warrants further investigation. Collectively, higher doses of CrM have shown beneficial effects for older adults with Alzheimer's Disease, young adults following acute periods of sleep deprivation, children suffering from TBI, and depression. The purpose of this narrative review is to (1) provide a comprehensive overview and rationale for the requirement of higher doses of CrM for brain bioenergetics, health and function and (2) identify areas of future research to further the field.

KEYWORDS: creatine; supplementation; brain bioenergetics; health; Alzheimer's disease; sleep deprivation; traumatic brain injury; depression

Received: 12 Jun 2025
Accepted: 17 Jul 2025
Published: 23 Jul 2025

INTRODUCTION

CrM is one of the most well-researched and effective ergogenic supplements for athletes [1]. Creatine is a nitrogenous compound derived from reactions involving the amino acids arginine, glycine and methionine, which are endogenously produced via a two-step process largely by the liver and brain [2]. Exogenously, creatine can be consumed

through dietary sources such as meat and seafood. Subsequently, those who adhere to vegetarian or vegan diets have approximately 30% lower intramuscular creatine content than those who consume meat and seafood [3]. An alternative form of exogenous creatine comes from CrM, the most bioavailable and effective formulation of creatine for increasing plasma and tissue creatine levels in skeletal muscle and the brain [4].

The brain, although only accounting for 2% of body mass, utilizes approximately 20% of energy consumption at rest [5]. Within the brain, neurons require a constant energy supply in the form of adenosine triphosphate (ATP) to maintain complex cellular processes such as synaptic functioning and neurotransmitter exocytosis [6]. When ATP releases energy to power cellular processes, it loses a phosphoryl group, converting it to adenosine diphosphate (ADP). Creatine, whether exogenously or endogenously sourced, interacts with the enzyme creatine kinase, where it gains a phosphate group and is stored as phosphocreatine (PCr). The primary function of PCr is to rapidly donate its phosphate group to ADP to quickly regenerate ATP. This rapid regeneration is important, since it is significantly faster than glycolytic processes and oxidative phosphorylation [2].

Over the past few decades, there has been a paradigm research shift from CrM for skeletal muscle and performance benefits to its effects on brain bioenergetics, health and function [5,7]. Although there is some (albeit mixed) evidence that brain creatine levels are responsive to CrM, speculation exists that higher doses (compared to those typically used for skeletal muscle improvements) may be necessary to produce consistent and/or significant increases in brain creatine levels across a variety of populations [7]. As such, the objective of this narrative review is to provide a comprehensive overview and rationale for considering higher doses of CrM to improve brain bioenergetics, health and function.

Creatine, Brain Bioenergetics and Cognition

The brain has extremely high energy demands relative to other bodily organs [5]. As a temporal and spatial high-energy phosphate-storage buffer, creatine plays a vital role, ensuring optimal function of the brain and cognitive processes [7]. The high baseline rate of brain metabolism coupled with increased metabolic costs of goal-directed cognition demonstrate a clear requirement for high energy supplements such as creatine [8].

In order to maintain a consistent creatine supply, the brain is dependent on a variety of creatine sources such as exogenous intake (from meat, seafood and supplementation) and production from the liver and brain [5]. Creatine is capable of crossing the BBB via microcapillary endothelial cells expressing the sodium- and chloride-dependent multi-pass membrane protein CT1, however at an attenuated rate relative to skeletal muscle [5]. This is evident by the lower levels of total creatine in the brain (4–5 mM) compared to that of skeletal muscle (35–40 mM) [7].

Creatine can also be endogenously synthesized within the brain via two enzymes expressed by brain cells (l-arginine:glycine amidinotransferase and guanidinoacetate N-methyltransferase) [2]. As such, the brain creatine system is partially independent from exogenous creatine sources. However, during times of prolonged metabolic stress (i.e., sleep deprivation) these cerebral stores may become depleted, forcing brain cells to rely on the slower glycolytic or oxidative phosphorylation pathways, potentially leading to mitochondrial dysfunction and impaired brain pathologies [9].

The importance of creatine for cognitive functioning is evident in creatine deficiency syndromes which result in depleted brain creatine stores [5]. Creatine deficiency syndromes are characterized by mental and neurodevelopmental disorders which are partially reversed through CrM supplementation [5]. In healthy adults, CrM improves measures of cognitive functioning, such as memory, attention time, and information processing speed [10]. In healthy older individuals, CrM has demonstrated improvements in short-term memory and intelligence/reasoning, but its effect on other cognitive domains remains unclear [11]. During mental fatigue, the supplementation of CrM (8 grams per day for 5 days) has demonstrated increased oxygen utilization in the brain and corresponding reduction of mental fatigue when subjects repeatedly perform a simple mathematical calculation [12]. The most robust evidence for the efficacy of CrM comes from acute periods of metabolic stressors such as sleep deprivation, hypoxia, and mentally fatiguing tasks; all representing times of increased brain metabolic demand [13]. Optimal CrM dosing protocols for improving brain bioenergetics, health and function are currently unknown, however preliminary evidence suggests that higher doses are likely needed to produce more consistent results compared to those commonly used in relation to skeletal muscle [13].

Consideration for Higher CrM Doses

There is evidence using magnetic resonance spectroscopy (MRS) that brain creatine levels increase in response to CrM supplementation. However, the magnitude of increase is approximately half that typically observed in skeletal muscle (approximately 10% vs. 20%) [13]. This discrepancy may be due to a compensatory response to exogenous creatine intake, whereby brain creatine endogenous synthesis decreases, which results in normalization despite supplementation. Further, given the lack of abundance of the CT1 protein in the BBB capillaries, the permeability of the brain to exogenous creatine is quite limited [5]. Assuming that the brain is resistant to creatine supplementation (either via normalization or reduced BBB transport), it is plausible that higher doses of CrM are likely required to increase and maintain brain creatine levels over time.

Rationale for the implementation of higher CrM doses likely stems from the landmark study by Dechent et al. in 1999 who showed, using P-MRS,

that a single-dose of 20 grams/day of CrM increased (non-statistically significant) total brain creatine content in 6 young healthy adults by ~3–7.7%. However, after 4 weeks of consuming 20 grams of CrM per day, there was a significant increase (~8.7%), with very high probability (p = 0.0008), in total brain creatine levels. Regional analyses found the largest increases in the thalamus (14.6%), white matter (11.5%), cerebellum (5.4%), and gray matter (4.7%). Beyond creatine, there were significant decreases in N-acetyle-containing compounds in the cerebellum and thalamus, and choline-containing compounds in the thalamus. Importantly, after 3 months of creatine cessation, all cerebral metabolic changes due to creatine supplementation were reversible [14]. However, in a more recent acute study using 31 P-MRS, Solis et al. (2017) failed to observe a statistically significant increase (Δ −0.7 to 3.9%) in brain PCr levels in young and older adults following 0.3 g/kg/day ~ or 25 grams of CrM for 7 days [15]. Similarly, in a recent study using functional near-infrared spectroscopy (fNIRS), Moriarty et al. (2023) did not observe a change cognitive performance or in prefrontal cortex activation in young adults supplemented with either 10 or 20 grams of CrM for 6 weeks [16]. Numerous other studies using lower creatine doses (i.e., 5 grams/day) for short durations found similar findings [13]. These findings point towards the need for higher doses and/or for prolonged periods of time to have noticeable changes in brain creatine levels. In the following sections we explore the impact of creatine dosing protocols across various disorders and their associated changes on brain creatine levels and clinical outcomes. As the brain creatine systems may vary across disorders, this precludes our ability to make inferences on the optimal blood creatine concentrations required to optimize brain creatine levels transdiagnostically.

Creatine and Alzheimer's Disease

Alzheimer's disease (AD) is the most common neurodegenerative disease with a rising prevalence, expecting to affect over 15 million Americans in 2050 [17]. Given the rising rates and lack of effective treatments, there is a growing need for interventions to reduce the symptom burden of AD [18]. Impaired brain metabolism is observed before and during the onset of symptoms, thus it has been hypothesized that bioenergetic decline contributes to the onset of diagnosis [19]. Particularly, in individuals with AD, there is a recognized dysfunction in the brain's creatine system. MRS studies have revealed decreased levels of PCr in the brains of individuals with AD, and in the later stages of AD, there is a significant reduction in the levels of brain-specific Cr kinase [17]. Moreover, people without dementia but possessing an apolipoprotein E epsilon 4 (APOE4) allele (the strongest genetic risk factor for AD) had lower brain Cr levels than noncarriers, which was correlated to worse cognitive test performance [17].

Recently, a pilot study (single-arm) by Smith et al., recruited 20 patients (73 years of age) with AD and provided them with 20 grams/day of CrM for 8 weeks [20]. Serum creatine levels were increased at weeks 4 and 8 (p < 0.001), and total brain creatine levels (as measured by H-MRS) increased by 11% (p < 0.001). Clinically, there were demonstrated improvements in cognition on global (p = 0.02) and fluid composites (p = 0.004), as well as List Sorting (p = 0.001), Oral Reading (p < 0.001) and Flanker tests (p = 0.05). Importantly, there were no adverse events evident from CrM. These findings demonstrate the feasibility of high dose, longer duration CrM supplementation to both increase brain creatine levels, but also improve cognitive outcomes in those with AD. However, the optimal dose and/or duration of CrM to improve brain bioenergetics and cognitive functioning in this population remains unknown.

Creatine and Sleep Deprivation

Sleep deprivation is increasingly common as a result of the modern lifestyle and has associations with chronic diseases and negative impacts on cognitive performance [21,22]. Sleep deprivation dysregulates cellular metabolism and energy homeostasis and has thus been deemed to be a 'metabolic disorder' [23]. In the brain, neurons enter a catabolic state during periods of sleep deprivation, which has downstream disruption on physiological functioning. This leads to impaired synaptogenesis and long-term memory, as the metabolically active cells shunt energetic resources away from processes which are not deemed to be essential, which includes a variety of cognitive functions [23].

As such, CrM may be able to compensate for some of the cognitive deficits observed from sleep deprivation, particularly at higher doses. A recent double-blind, randomized, cross-over design trial by Gordji-Nejad et al., administered a single high dose (0.35 g/kg) of CrM in 15 healthy adults prior to undergoing 21 h of sleep deprivation [24]. Two consecutive ^{31}P-MRS scans, 1H-MRS, and cognitive tests were performed at baseline (prior to CrM ingestion), and again at 3, 5.5, and 7.5 h after CrM administration. Brain PCr levels significantly increased and there was a reduction in subjective fatigue compared to placebo during sleep deprivation. Further, creatine was found to alleviate changes in phosphates, pH and cognitive performance associated with sleep deprivation [24]. Although it is promising to see brain creatine levels increase after a single higher dose, a recent pilot study by Todorovic et al., suggest a complex relationship between sleep deprivation and creatine metabolism, whereby serum creatine levels significantly increased post 24 h sleep deprivation, contrary to the initial hypothesis [25]. Unfortunately, brain creatine levels were not determined in this study. However, the increased serum concentration of creatine may indicate diminished cerebral intake of creatine or increased efflux of brain-derived creatine into the circulation while sleep deprived, which warrants further

investigation. Both of the above mechanisms could rationally be overcome by higher doses of creatine, however further research is required.

Creatine and Traumatic Brain Injury

In the general adult population, approximately 12% of people have a history of TBI [26]. A TBI is associated with an uncoupling of energy supply and demand due to altered cerebral energy availability, with a reduction in brain creatine levels [7,27]. As such, creatine supplementation (whether proactive or post-injury) has been suggested to be protective and enhance recovery in TBI [13].

An open-label randomized controlled trial by Sakellaris et al., in 39 children and adolescents administered a high dose (0.4 grams/kg per day) of CrM for 6 months, which demonstrated numerous beneficial effects [28]. Particularly, there were improvements in several parameters including, duration of post-traumatic amnesia, duration of intubation, length of intensive care unit stay, disability, recovery, self-care, communication, locomotion, sociability, personality/behaviour, and neurophysical/cognitive functioning [28]. Oxygen deprivation is a model which can mimic the effects of TBI [13]. As such, Turner et al., conducted a randomized, double-blind, crossover trial whereby 15 healthy adults were supplemented with 20 g CrM and placebo treatments for 7 days [29]. A hypoxic gas mixture was administered for 90 min, causing global oxygen deficit and impairing a range of neuropsychological processes. Brain creatine levels increased by 9.2% and the hypoxia-induced decrements in cognitive performance were restored with creatine supplementation [29].

Creatine and Depression

The prevalence of depression has been increasing with over 290 million people with a documented depression diagnosis globally [30]. The primary treatment modalities for depression include antidepressants and therapy, however a considerable portion of the population (30–50%) does not respond to these standard treatments [31]. As such, additional adjunctive treatment modalities, such as creatine, have garnered attention [9,32]. At a population-level, a study of 22,692 U.S. adults found an inverse, stepwise association between dietary creatine intake and depression [33]. Although dietary creatine is important, one would need to eat approximately 3 pounds of beef in order to get around 5 g of creatine; therefore, creatine supplementation presents a more viable route [34].

While the majority of studies using creatine as a treatment for depression used doses ≤ 5 g per day, Kondo et al., randomized participants to receive either CrM 2, 4 or 10 g daily for 8 weeks, and conducted pre- and post-treatment phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) scans to measure frontal lobe PCr [35]. The frontal lobe PCr increased by 4.6, 4.1 and 9.1% in the 2, 4 and 10 g groups, respectively; here we see a double in brain creatine levels from 4 g to 10 g daily, whereas the brain creatine levels remained relatively unchanged from 2 g to 4 g. Further,

regression analyses of the PCr and depression scores demonstrated that frontal lobe PCr was inversely correlated to depression scores [35]. These findings demonstrate that higher creatine doses are associated with higher brain creatine levels which are associated with greater antidepressant response.

Other Strategies to Increase Brain Creatine Levels

Beyond increasing the dose and/or duration of CrM, there are some other strategies which may be promising to increase brain creatine levels. Firstly, there is some evidence that short-term (4 weeks) supplementation with guanidinoacetic acid (GAA; 3 grams/day), a direct natural precursor to creatine, is superior to CrM (3.4 grams/day) for increasing muscle and brain creatine levels in healthy young males [34]. The authors speculate that GAA has preferable uptake by target tissues via various mechanisms involving GAA transport kinetics [36]. Second, cyclocreatine (creatine analog) administration in mice has demonstrated improvements in brain bioenergetics in a mode of CT1 deficiency, demonstrating its ability to presumably bypass the BBB [37]. Third, intranasal creatine administration in rats has been shown to increase brain creatine and performance levels more so than oral supplementation, however no data yet exists in humans [38]. Fourth, prolonged exogenous creatine intake downregulates CT1, potentially leading to resistance or attenuated response after ongoing consumption [39]. As such, methods to modulate CT1 function are of particular interest, such as glucocorticoid-regulated kinases, mammalian target of rapamycin, ammonia, and Klotho protein [40]. While the above strategies may be promising, there is a need for further research to delineate the net effect of high dose and long-term creatine intake on brain creatine intake, endogenous creatine synthesis and CT1 activity.

CONCLUSIONS

Overall, there has been a paradigm research shift from CrM for skeletal muscle benefits to its potential to improve brain bioenergetics, health and function. Although there is evidence that brain creatine levels are responsive to exogenous supplementation, emerging evidence demonstrates that higher and/or longer dosing strategies may be required. However, the optimal protocol is unknown. Higher doses of CrM have provided some benefits in older adults with AD, young adults undergoing sleep deprivation, in children and adolescents experiencing TBI, and in those experiencing depression. Future research is required to determine the optimal CrM supplementation protocol needed to increase brain creatine levels (including regional brain areas) in a variety of healthy and clinical populations.

ETHICAL STATEMENT

Ethics Approval

Not applicable.

Declaration of Helsinki STROBE Reporting Guideline

This study adhered to the Helsinki Declaration. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guideline was followed.

DATA AVAILABILITY

No data were generated from the study.

AUTHOR CONTRIBUTIONS

DC & NF conceptualized the idea. NF wrote the first draft of the manuscript. DC critically reviewed and edited the manuscript. All authors approved the final version of the manuscript prior to submission.

CONFLICTS OF INTEREST

DC has conducted industry-sponsored research involving creatine supplementation and received creatine donations for scientific studies and travel support and speaking honoraria for presentations involving creatine supplementation at scientific conferences and on social media. In addition, DC serves on the Scientific Advisory Board for Alzchem and Create (companies that manufacture creatine products) and as an expert witness/consultant in legal cases involving creatine supplementation. NF declares no conflicts of interest.

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How to cite this article:
Fabiano N, Candow D. Creatine supplementation: More is likely better for brain bioenergetics, health and function. J Psychiatry Brain Sci. 2025;10(4):e250006. https://doi.org/10.20900/jpbs.20250006.