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CREATINE FUNCTION IN THE CENTRAL NERVOUS SYSTEM: IMPACT ON COGNITIVE PERFORMANCE AND MENTAL HEALTH – A COMPREHENSIVE REVIEW

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ABSTRACT

Creatine monohydrate is a nitrogenous organic acid historically recognized for its ergogenic role in skeletal muscle energy metabolism (Allen, 2012). However, recent literature emphasizes its critical function within the central nervous system (CNS), where the brain, representing only 2% of total body mass, consumes approximately 20% of resting energy (Forbes et al., 2022; Gualano et al., 2016). The creatine kinase (CK)/phosphocreatine (PCr) system serves as a primary temporal and spatial energy buffer, facilitating the rapid regeneration of adenosine triphosphate (ATP) during periods of high metabolic demand (Allen, 2012; Dolan et al., 2018; Merege-Filho et al., 2017). This comprehensive review synthesizes evidence from 32 provided scientific sources to evaluate the impact of creatine supplementation on cognitive performance and mental health. While effects in healthy, well-rested individuals are often subtle or inconsistent, creatine demonstrates significant efficacy in restoring cognitive function during states of metabolic stress, including sleep deprivation, hypoxia, and aging (Allen, 2012; Dolan et al., 2018; Prokopidis et al., 2022). Furthermore, clinical data suggest that creatine acts as a potent adjunctive therapy for major depressive disorder (MDD) by addressing underlying bioenergetic deficits (Juneja et al., 2024; Sherpa et al., 2025). Emerging research also highlights creatine's neuroprotective potential in recovery from traumatic brain injury (TBI) and its influence on hippocampal structural plasticity (Dolan et al., 2018; Gerbatin et al., 2019; Zhu et al., 2025). This review addresses metabolism, cognitive domains, psychiatric implications, and underlying mechanisms, establishing creatine as a multifaceted modulator of brain health.

KEYWORDS

Creatine Monohydrate, Brain Bioenergetics, Cognitive Performance, Major Depressive Disorder, Neuroprotection, Sleep Deprivation

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1. Introduction

Creatine (α -methyl-guanidino-acetic acid) is a naturally occurring compound synthesized from the amino acids arginine, glycine, and methionine (Allen, 2012; Avgerinos et al., 2018; Vietor et al., 2025). While approximately 95% of the body's creatine is stored in skeletal muscle, the remaining 5% is distributed in high-energy-demanding tissues, primarily the brain (Allen, 2012; Dolan et al., 2018; Han et al., 2025). The human brain relies heavily on a constant supply of ATP to maintain electrical membrane potentials, drive synaptic signaling, and support neurotransmitter exocytosis (Dolan et al., 2018; Forbes et al., 2022).

The Cr-PCr circuit functions as a metabolic "rheostat," maintaining energy homeostasis when ATP demand exceeds the rate of oxidative phosphorylation (Su, 2025). Given that metabolic dysfunction and mitochondrial impairment are leading hypotheses in the pathogenesis of both cognitive decline and psychiatric disorders, interventions that modulate brain energetics are of high clinical interest. Creatine supplementation has been shown to increase brain creatine levels by 3–10%, although the blood-brain barrier (BBB) presents a significant obstacle to uptake compared to peripheral tissues (Dolan et al., 2018; Moriarty et al., 2023). This review explores the extent to which this increase in cerebral creatine translates to improved cognitive outcomes and psychological well-being across the lifespan.

2. Methodology

This study is a literature review conducted according to the principles of evidence-based medicine. A structured search was performed between March and June 2026 using PubMed/MEDLINE, Google Scholar, and Scopus. The primary search terms used were: "creatine monohydrate," "supplementation," "brain," "mental health," "cognition," and "creatine metabolism." Terms were combined using Boolean operators (AND, OR).

Inclusion criteria required research investigating the effects of oral creatine monohydrate supplementation on human participants, including healthy individuals across the lifespan (adults and the elderly) and clinical populations with conditions such as major depressive disorder (MDD), bipolar disorder, post-traumatic stress disorder (PTSD), and traumatic brain injury (TBI). The review prioritized double-blind, randomized controlled trials (RCTs), systematic reviews, and meta-analyses to maintain the highest level of clinical evidence. To ensure the inclusion of the most up-to-date scientific evidence, the literature search primarily focused on studies published within the last ten years. Nevertheless, some earlier studies were retained because of their seminal importance and enduring relevance to the topic under investigation.

The methodology focused on studies providing objective measures of brain health. These outcomes included cognitive test scores (e.g., Raven's Matrices, Digit Span, Stroop test), clinical psychiatric scales (e.g., PHQ-9, POMS), and cerebral metabolic markers assessed via Magnetic Resonance Spectroscopy (MRS) or near-infrared spectroscopy (fNIRS). Preclinical animal models were selectively included when they provided essential mechanistic insights into mitochondrial function, antioxidant activity, or structural plasticity not fully elucidated in human trials.

Exclusion criteria involved studies utilizing multi-ingredient supplements where the specific effects of creatine could not be isolated, non-randomized designs (unless providing unique case insights), and research with incomplete post-intervention data. A total of 33 provided sources were synthesized to form this comprehensive review.

3. Mechanisms Linking Creatine to Brain Function

Creatine influences brain function through several proposed pathways:

Bioenergetic Support: It maintains ATP levels, preventing "energy crashes" during neuronal stimulation (Allen, 2012; Gordji-Nejad et al., 2026; Juneja et al., 2024).

Antioxidant Activity: Creatine directly scavenges hydroxyl radicals ($\cdot\text{OH}$) and prevents mitochondrial permeability transition (Marques & Wyse, 2019; Tran et al., 2022).

Neuromodulation: It may act as a central neurotransmitter or neuromodulator, interacting with GABAA and NMDA receptors to regulate excitability (Braissant et al., 2011; Gordji-Nejad et al., 2026; Meftahi et al., 2023).

Structural Plasticity: Long-term supplementation upregulates hippocampal structural plasticity, increases BDNF levels, and enhances the density of GABA neurons (Jeryous Fares et al., 2026; Zhu et al., 2025).

4. Creatine Metabolism in the Central Nervous System

4.1 Endogenous Synthesis and Transport

Creatine synthesis follows an inter-organ pathway beginning in the kidneys, where L-arginine:glycine amidinotransferase (AGAT) catalyzes the formation of guanidinoacetate (GAA) from arginine and glycine (Geng et al., 2024). GAA then enters the liver, where guanidinoacetate N-methyltransferase (GAMT) utilizes S-adenosylmethionine (SAME) to methylate GAA into creatine. This process is metabolically demanding, consuming between 40% and 70% of available methyl groups provided by SAME (Allen, 2012).

Unlike skeletal muscle, which lacks synthesis enzymes, the brain possesses its own machinery for endogenous creatine production (Allen, 2012; Dolan et al., 2018; Juneja et al., 2024). AGAT and GAMT are expressed in neurons, astrocytes, and oligodendrocytes, suggesting a degree of independence from peripheral sources (Braissant et al., 2011; Dolan et al., 2018). However, transport from the periphery still occurs via the SLC6A8 transporter, though its expression at the BBB is limited, restricting the rate of exogenous uptake (Geng et al., 2024). Genetic deficiencies in AGAT, GAMT, or the SLC6A8 transporter result in severe neurological symptoms, including intellectual disability and seizures, underscoring the absolute necessity of creatine for brain health (Joncquel-Chevalier Curt et al., 2015).

4.2 The Energy Buffer System

Within the CNS, creatine is reversibly phosphorylated into PCr by the enzyme creatine kinase (CK). The brain-specific isoform, BB-CK, is essential for maintaining ATP levels during rapid neural firing (Andres et al., 2008). This PCr-ATP shuttle allows the brain to regenerate energy up to 12 times faster than oxidative phosphorylation. PCr acts as a smaller, less negatively charged molecule than ATP, allowing for faster diffusion to sites of demand (Han et al., 2025). During initial neuronal stimulation, an "initial dip" in PCr occurs to maintain stable ATP concentrations (Toniolo et al., 2017).

5. Creatine and Cognitive Performance

5.1 Memory

Creatine supplementation has shown varying effects on memory, largely dependent on age and baseline metabolic status (Allen, 2012; Forbes et al., 2022; Prokopidis et al., 2022). A systematic review and meta-analysis of 10 RCTs concluded that creatine significantly improves measures of memory in healthy humans. Subgroup analyses revealed that these benefits are most robust in older adults (66–76 years), where supplementation may provide the additional energy required for aging neurons to complete cognitive tasks (Prokopidis et al., 2022).

In young adults, memory improvements are less consistent. Moriarty et al. (2023) found no improvement in episodic memory in young participants following six weeks of supplementation. However, individuals with lower baseline creatine levels, such as vegetarians and vegans, often show more pronounced memory enhancements after supplementation. For example, Rae et al. (2003) demonstrated improved working memory in vegetarians taking 5 g/day for six weeks.

5.2 Executive Function

The impact on executive function—including tasks like reasoning, logic, and planning—appears to be task-dependent (Dolan et al., 2018). Some studies report improvements in intelligence scores and abstract reasoning, particularly when tasks are completed under time pressure (Avgerinos et al., 2018). Bayesian evidence in a large study supported a small beneficial effect of creatine on cognitive performance, though results for Raven's Advanced Progressive Matrices (RAPM) did not always reach frequentist significance (Sandkühler et al., 2023). In contrast, several meta-analyses found no significant overall improvement in executive function across broad populations, suggesting its role may be limited to situations of extreme cognitive demand (Xu et al., 2024).

5.3 Attention and Processing Speed

Recent meta-analytical data suggest that creatine can markedly accelerate information processing speed. In physically active men, a 7-day loading phase (20 g/day) significantly improved cognitive performance on the digit cancellation test (DCT), indicating enhanced attention and speed. Turner et al. (2015) also noted that creatine offset decrements in complex attention during physiological stress (Dolan et al., 2018; Xu et al., 2024).

5.4 Sleep Deprivation, Stress, and Fatigue

The cognitive-enhancing properties of creatine are most evident when brain energetics are compromised (Dolan et al., 2018). **Sleep Deprivation:** Total sleep deprivation (24–36 hours) leads to a decline in processing speed and executive function. Single high doses of creatine (0.35 g/kg or 0.2 g/kg) have been shown to attenuate these deteriorations. Creatine administration balances the hemispheric asymmetry in energy consumption typically induced by sleep loss (Allen, 2012; Gordji-Nejad et al., 2026).

Hypoxia: Under low-oxygen conditions (e.g., 10% oxygen), creatine supplementation restores corticomotor excitability and prevents the typical decline in cognitive task accuracy (C.E. Turner et al., 2015).

Mental Fatigue: Creatine supplementation has been found to mitigate the effects of mental fatigue, specifically improving accuracy during prolonged, cognitively demanding tasks such as a 90-minute Stroop test (Van Cutsem et al., 2020). Additionally, earlier evidence suggests that creatine loading can reduce subjective feelings of mental exertion during repetitive stressful cognitive assessments (Watanabe et al., 2002).

6. Creatine and Mental Health

6.1 Depression

Mitochondrial dysfunction and impaired bioenergetics are transdiagnostic features of depression (Han et al., 2025; Juneja et al., 2024; Sherpa et al., 2025). Observational studies have identified a significant negative relationship between dietary creatine intake and the risk of depression in U.S. adults (Allen, 2012; Jeryous Fares et al., 2026). Clinical trials demonstrate that creatine (5–10 g/day) as an adjunct to Selective Serotonin Reuptake Inhibitors (SSRIs) can accelerate treatment response, sometimes as early as week two. These effects appear more pronounced in female and adolescent patients with treatment-resistant depression. Combining creatine with Cognitive Behavioral Therapy (CBT) has also shown superior symptom reduction compared to CBT alone (Sherpa et al., 2025).

6.2 Anxiety and PTSD

Evidence regarding anxiety is more limited but suggestive of localized creatine deficits in the prefrontal cortex of patients with social anxiety and panic disorder. Preliminary open-label studies in treatment-resistant PTSD found that 5 g/day of creatine significantly improved sleep quality and reduced PTSD symptoms (Jeryous Fares et al., 2026).

6.3 Bipolar Disorder

Creatine use in bipolar disorder requires extreme caution. While it may improve verbal fluency in the depressive phase (Toniolo et al., 2017), there are documented cases of creatine-induced hypomania or manic switch (Roitman et al., 2007). It is generally considered a potential contraindication unless used under strict psychiatric supervision.

6.4 Inborn Errors of Creatine Metabolism and Neurodegenerative Conditions

6.4.1 Primary Creatine Deficiency Syndromes (CDS)

Primary creatine deficiency syndromes represent a group of rare genetic disorders that highlight the absolute necessity of creatine for normal brain development and cognitive function. These syndromes arise from mutations in the genes responsible for creatine biosynthesis-L-arginine:glycine amidinotransferase (AGAT) and guanidinoacetate N-methyltransferase (GAMT) or from defects in the X-linked creatine transporter (SLC6A8). Clinical manifestations typically emerge in early infancy and include global developmental delay, severe intellectual disability, speech and language impairments, autism, and refractory epilepsy. Magnetic Resonance Spectroscopy (MRS) in these patients reveals a near-complete absence or a profound decrease in the brain creatine signal (Allen, 2012; Braissant et al., 2011).

Therapeutic outcomes vary significantly based on the specific genetic defect. Patients with AGAT and GAMT synthesis deficiencies often show substantial clinical and neurological improvement following long-term, high-dose oral creatine monohydrate supplementation (0.30–0.80 g/kg/day), which can partially or fully restore brain creatine levels and reduce seizure frequency. Early intervention is particularly critical, as presymptomatic treatment in neonates can prevent many of the devastating neurodevelopmental consequences. Conversely, oral supplementation is largely ineffective in treating SLC6A8 transporter defects because the deficiency prevents the compound from crossing the blood-brain barrier and entering neurons (Braissant et al., 2011; Marques & Wyse, 2019).

6.4.2 Alzheimer's Disease and Cognitive Aging

Emerging research suggests that creatine may serve as a neuroprotective agent in the context of cognitive aging and neurodegenerative dementias like Alzheimer's disease (AD). In AD patients, the brain-specific isoform of creatine kinase (BB-CK) is significantly inactivated by oxidative stress, and creatine has been found to deposit within amyloid-beta ($A\beta$) plaques. Preclinical studies indicate that creatine protects hippocampal neurons from $A\beta$ -induced toxicity and glutamate excitotoxicity by stabilizing mitochondrial membrane potential and reducing the generation of reactive oxygen species (Marques & Wyse, 2019).

In animal models of AD, long-term creatine supplementation has been shown to improve spatial cognition, modulate $A\beta$ and tau protein processing, and upregulate proteins associated with neural plasticity (Zhu et al., 2025). In humans, while data for diagnosed AD populations are currently limited, studies in healthy older adults (66–76 years) demonstrate that creatine loading (e.g., 20 g/day for 7 days) can improve measures of memory and abstract reasoning (Prokopidis et al., 2022). These benefits are likely due to creatine providing the additional bioenergetic support required by the aging brain to complete cognitively demanding tasks (Avgerinos et al., 2018).

6.4.3 Other Neurodegenerative Contexts

Creatine has also been extensively investigated in Huntington's disease (HD) and Parkinson's disease (PD), conditions where energy metabolism is chronically compromised. In HD, creatine supplementation has been shown to lower brain glutamate levels and reduce oxidative damage biomarkers. However, while early phase II biomarker trials showed that high-dose creatine could reduce cortical and striatal atrophy, subsequent large-scale phase III trials (e.g., CREST-E) were halted for futility. Similarly, in PD, despite animal models showing protection of dopaminergic neurons, human clinical trials have failed to definitively show a delay in disease progression (Forbes et al., 2022; Marques & Wyse, 2019). These findings suggest that while creatine is a potent bioenergetic stabilizer, its clinical utility in neurodegeneration may be most effective when used prophylactically or as an early-stage adjunct rather than a primary treatment for advanced pathology.

6.5 Neuroprotection

Traumatic Brain Injury (TBI) and concussions induce a "metabolic crisis" characterized by hypometabolism and mitochondrial failure. Supplementation in children and adolescents following TBI has reduced post-traumatic symptoms, including dizziness, headaches, and fatigue (Vietor et al., 2025). In animal models, creatine reduces cortical contusion volume by up to 50% (Dolan et al., 2018; Geng et al., 2024). It protects parvalbumin-positive GABAergic neurons, which may reduce long-term seizure susceptibility following injury. It also mitigates oxidative stress responses following umbilical cord occlusion in fetal sheep (Tran et al., 2022).

7. Discussion

The evidence collectively indicates that creatine is more than an ergogenic aid for muscle; it is a vital metabolic regulator in the CNS. Its efficacy as a cognitive enhancer is highly "state-dependent," offering maximal benefits when the brain's energy status is challenged—such as during aging, hypoxia, or acute sleep deprivation (Dolan et al., 2018).

One significant challenge is the BBB's limited permeability to oral creatine, which necessitates higher or more prolonged dosing to achieve measurable increases in brain tissue (3–10%) (Moriarty et al., 2023). Standard loading phases (20 g/day for 5–7 days) followed by maintenance (5–10 g/day) are recommended to reach therapeutic brain levels (Bakian et al., 2020; Gualano et al., 2016). Furthermore, dietary habits play a crucial role, as vegetarians—who have lower baseline stores—consistently show a more robust cognitive response. Regarding safety, meta-analyses confirm that standard doses do not cause renal damage in healthy individuals (de Souza e Silva et al., 2019).

Future research should prioritize several critical areas to fully elucidate the therapeutic potential of creatine in the central nervous system. A primary focus must be placed on optimizing dosing strategies or exploring precursors such as guanidinoacetic acid to more effectively bypass the blood-brain barrier and increase cerebral concentrations. Additionally, long-term, multi-year trials in geriatric populations are essential to confirm the efficacy of creatine in preventing or delaying neurodegenerative decline. There is also a significant need for precise dose-response mapping to identify the specific metabolic thresholds required for clinical improvement across various psychiatric disorders.

10. Conclusion

Creatine monohydrate is a safe, inexpensive, and effective supplement for enhancing brain bioenergetics. Its ability to counteract cognitive deterioration under stress and its potential as a psychiatric adjunct suggest broad applications in both clinical and social settings. While young, well-rested individuals may see minimal benefits, the neuroprotective and mood-modulating properties of creatine offer a promising frontier for managing aging, depression, and brain injury recovery.

Conflict of Interest Statement: No conflicts of interest to declare.

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