International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	CREATINE SUPPLEMENTATION AS A STRATEGY FOR COGNITIVE SUPPORT AND NEUROPROTECTION
DOI	https://doi.org/10.31435/ijitss.2(50).2026.5794
RECEIVED	20 February 2026
ACCEPTED	11 June 2026
PUBLISHED	16 June 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

CREATINE SUPPLEMENTATION AS A STRATEGY FOR COGNITIVE SUPPORT AND NEUROPROTECTION

Agata Ławniczak *(Corresponding Author, Email: agatalawniczak12@gmail.com)*
Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0008-1588-4298

Jagoda Prządka
Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0001-7921-919X

Anna Tomaszewska
Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0004-4330-0780

Marcelina Kaczmarek
Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0009-0114-0607

Maria Pojawa
Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0003-9544-8106

Natalia Łazor
Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0003-6709-5577

Wioletta Witkowska
Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0003-4814-3350

Ewelina Wagner
Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0009-0741-1295

Aleksandra Chudzik
Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0000-2598-1261

Emilia Buzek
Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0001-5597-828X

ABSTRACT

Creatine (methylguanidine-acetic acid) is an organic compound formed from reactions involving the amino acids arginine, glycine and methionine. Synthesized endogenously in the kidneys and liver, it is concentrated in skeletal muscle and tendons, as well as in the brain, liver, kidneys and testes. Since the 1990s, creatine has been a widely used sports supplement, known to enhance muscle strength, endurance and recovery. It is one of the most extensively researched supplements in the world, and its efficacy and safety profile have been confirmed in thousands of peer-reviewed publications. With an increasing number of publications highlighting the effects of creatine on the central nervous system (CNS), this article aims to review the most recent literature.

Objective: This review evaluates scientific evidence concerning creatine's effects on cognitive function and neuroprotection in healthy adults while analyzing the underlying neurobiological mechanisms.

Methodology: A literature review was performed using PubMed, Scopus, and Google Scholar, encompassing meta-analyses, randomized controlled trials, and neuroimaging data.

Results: Analysis of the current literature indicates that creatine supplementation can increase brain phosphocreatine levels, thereby enhancing cellular bioenergetics. In healthy adults, improvements in short-term memory, fluid intelligence, and reduced mental fatigue represent the most pronounced cognitive benefits observed primarily under conditions of metabolic stress, including sleep deprivation or demanding cognitive tasks.

Conclusions: Creatine represents a promising, safe intervention for supporting CNS function. Especially since its safety and effectiveness have been extensively studied. However, further research must establish definitive dosing protocols to optimize cognitive outcomes.

KEYWORDS

Creatine Monohydrate, Supplementation, Cognitive Function, Neuroprotection, Neuroplasticity, Blood-Brain Barrier

CITATION

Agata Ławniczak, Jagoda Prządka, Anna Tomaszewska, Marcelina Kaczmarek, Maria Pojawa, Natalia Łazor, Wioletta Witkowska, Ewelina Wagner, Aleksandra Chudzik, Emilia Buzek. (2026) Creatine Supplementation as a Strategy for Cognitive Support and Neuroprotection. *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.5794

I. Introduction

Creatine is a substance produced from the amino acids arginine, glycine, and methionine. This endogenous production takes place primarily in the kidneys and liver. It can also be supplied to the body exogenously through our diet. The richest natural sources are red meat and fish, though dietary supplements have become an increasingly common way to boost intake. Once synthesized or absorbed, it is transported to tissues with high energy requirements, such as the brain, skeletal muscle, and the testes [Almeida et al., 2006].

Today, creatine holds the title of the most extensively researched dietary supplement and in recent years its popularity has been growing not only among professional athletes but also among amateurs. It has evolved from a specialized tool for elite performance into a mainstream staple for anyone looking to improve their physical resilience and cognitive longevity.

1.1 Molecular and metabolic foundations of creatine action

At the molecular level, creatine binds with phosphate molecules to form phosphocreatine (PCr), which serves as the primary energy substrate for ATP resynthesis during intense physical exertion. Through the action of creatine kinase (CK), a phosphate group is transferred from phosphocreatine to ADP, leading to the regeneration of ATP [Avgerinos et al., 2018]. Creatine mechanisms of action involves also spatial energy buffering and transferring energy from the mitochondria to the cytosol. This is a key mechanism for maintaining ATP homeostasis at the cellular level and preparing the body for physical exertion. [Sahlin & Harris, 2011].

Additionally, creatine exhibits an antioxidant effect by scavenging reactive oxygen species (ROS) in an acellular environment [Sestili et al., 2011].

II. Methodology

This study conducted a literature review to synthesize the latest biochemical and clinical data, as well as neuroimaging findings, regarding the effects of creatine supplementation on brain function. The review includes reports from peer-reviewed clinical trials, meta-analyses, and also proton magnetic resonance spectroscopy (^{1}H-MRS) studies, capturing recent advancements in the field up to the years 2004–2025. Data were extracted based on their relevance to CNS bioenergetics and cognitive performance. When selecting the relevant literature, the focus was on studies involving healthy adult populations. Moreover, the work aims to isolate the mechanisms by which creatine improves brain function and to summarize clinical trial results on improvements in working memory, reasoning, and performance maintenance under metabolic stress. The review also included research evaluating how specific dietary habits (e.g., plant-based vs. omnivorous diets) influence the efficacy of supplementation. Because the primary objective is to assess cognitive optimization in healthy individuals, any studies focusing on the therapeutic treatment of diagnosed neurological diseases or psychiatric disorders were excluded from this analysis.

III. Effect on The Central Nervous System

3.1. Neurological foundations of the brain as a high-energy system

In addition to its effects on physical performance, the central nervous system also has a high metabolic demand. Although it accounts for only a small percentage of the body's mass, it consumes approximately 20% of the body's glucose and oxygen [Rae et al., 2003]. A continuous supply of ATP is necessary for optimal brain function. This supply is vital for maintaining the integrity of neuronal membranes, for ion transport, for neurotransmitter synthesis, and for cognitive processes such as memory and learning.

Consistent with skeletal muscle, neurons and glial cells actively utilize the CK/PCr system [Wyss & Kaddurah-Daouk, 2000]. The primary form of creatine kinase present in the brain is the CK-BB type. This localized energy-buffering system is indispensable for efficient synaptic energy management, as rapid ATP replenishment is essential for neurotransmitter reuptake and the maintenance of postsynaptic potentials. Given that synaptic activity—the very foundation of cognitive function—relies on near-instantaneous energy access, the phosphocreatine (PCr) pool serves as the primary metabolic guarantor for these processes [Hemmer & Wallimann, 1993]. Beyond mere energy supply, the CK/PCr system plays a critical role in preventing depletion. By stabilizing the ATP/ADP ratio and preserving mitochondrial membrane potential during periods of heightened neuronal firing, it effectively shields neurons from energetic exhaustion and subsequent cellular stress [O'Gorman et al., 1997].

Therefore, optimizing CNS creatine concentrations, especially through supplementation, may enhance neuronal function and synaptic plasticity [Bürli et al., 2013]. This connection between creatine supply and energetic stability in key brain structures, such as the hippocampus, provides the neurobiological basis for its potential as a cognitive-enhancing agent in healthy individuals.

3.2. Transport of creatine to the central nervous system

Research indicates that the adult CNS possesses a limited capacity for creatine uptake from circulation [Schultze A., 2003], with the creatine transporter CT1 (SLC6A8) at the blood-brain barrier (BBB) playing a critical role in regulating brain creatine levels as the primary transport pathway [Dechent et al., 1999]. Additionally, brain cells express the two enzymes necessary for creatine synthesis—arginine:glycine amidinotransferase (AGAT) and guanidinoacetate N-methyltransferase (GAMT)—during both development and adulthood. This suggests that brain creatine levels may be partially independent of exogenous sources, including dietary intake [Braissant et al., 2011]. However, in instances where brain creatine levels are low or restricted, supplementation can positively influence concentrations across a range of neurological conditions [Snow et al., 2024].

Over 95% of the body's creatine is stored in skeletal muscle, but it is also synthesized in the liver, pancreas, and kidneys, entering circulation and muscle via the SLC6A8 transporter. Dietary and supplemental creatine use the same pathway. The brain's ability to synthesize creatine endogenously [Rochel et al., 2021] makes it less responsive to external sources. The lack of SLC6A8 in astrocytes may further limit brain uptake of exogenous creatine [Braissant et al., 2011]. The brain likely relies on endogenous synthesis unless availability is disrupted, either acutely (e.g., sleep deprivation, intense exertion) or chronically (e.g., aging, brain injury, depression, Alzheimer's disease). Low brain creatine levels also accompany several neurodegenerative diseases, where the magnitude of the deficit often correlates with the severity of the disorder [Balestrino M., 2021].

3.3. The mechanism of action of creatine on a neuron

The physiological mechanism of creatine in neurons involves optimizing energy management and stabilizing cellular structures, where the CK/PCr system plays a critical role as a buffer and transporter of high-energy phosphates [Wallimann et al., 1992]. Through immediate rephosphorylation of ADP, creatine ensures a continuous supply of ATP for the Na+/K+-ATPase enzyme, which is essential for maintaining resting membrane potential, efficient restoration of ionic gradients, and preservation of calcium (Ca2+) homeostasis, thereby protecting the cell from excitotoxicity [Wallimann et al., 1992]. Furthermore, the CK system governs the proper migration of neuronal growth cones and the elongation of axons and dendrites, thereby directly influencing the efficacy of synaptic plasticity and long-term potentiation (LTP) [Perasso et al., 2013].

Recent studies show that creatine also acts as a neuromodulator and co-transmitter, modulating postsynaptic GABA receptors and helping control the activity of brain networks [Bürli et al., 2013]. Creatine also affects appetite and body weight by acting on certain parts of the hypothalamus [Galbraith et al., 2006]. In mitochondria, creatine helps stabilize the mPTP (mitochondrial permeability transition pore), making neurons more resistant to stress [O'Gorman et al., 1997].

The CK/PCr system acts as a "phosphocreatine shuttle" in the CNS, connecting mitochondrial energy production with sites of high consumption, such as ion pumps and synaptic vesicles [Wallimann et al., 1992]. Because neurons have long distances between the cell body and axon terminals, phosphocreatine, which diffuses faster than ATP, serves as the main carrier of high-energy phosphates needed for synaptic transmission [Wallimann et al., 1992]. During intense cognitive load, rapid ATP depletion is countered by creatine kinase, which instantly rephosphorylates ADP using the phosphocreatine pool, stabilizing the ATP/ADP ratio. This prevents ADP accumulation that would otherwise inhibit ATPases and reduce neuronal firing efficiency [Rae et al., 2003].

3.4. Mitochondrial impact and neuroprotection

Creatine, through its mitochondrial isoform (mtCK), stabilizes the mPTP in an octameric state, preventing cytochrome c release and protecting neurons from apoptosis [O'Gorman et al., 1997]. It also provides direct and indirect antioxidant effects in mitochondria, reducing superoxide production and protecting mitochondrial DNA (mtDNA) from oxidative damage. This antioxidant capacity is essential for maintaining the mitochondrial respiratory chain in high-energy-demand tissues such as the brain [Guidi et al., 2008].

3.5. Creatine as a neuromodulator

To formally meet the strict criteria of a neuromodulator, a molecule must be concentrated in synaptic terminals and released into the synaptic cleft upon neuronal depolarization. Recent studies have demonstrated that creatine fulfills these exact parameters; it is actively concentrated and stored within synaptic vesicles and undergoes stimulus-evoked, calcium (Ca2+)-dependent exocytosis during action potentials [Bürli et al., 2013]. Once released into the synaptic cleft, creatine exerts direct allosteric modulatory effects on key neurotransmitter receptors, bridging the gap between cellular bioenergetics and electrical signaling. Specifically, it has been shown to interact with both major inhibitory and excitatory networks by modulating the activity of γ-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors. By fine-tuning the postsynaptic responsiveness of these receptors, extracellular creatine directly influences synaptic plasticity—facilitating processes such as long-term potentiation (LTP) and long-term depression (LTD)—which form the foundational neurochemical basis for memory consolidation and cognitive adaptability [Bürli et al., 2013]. Furthermore, creatine's role extends to glial cells, particularly astrocytes, which are responsible for managing the brain's glutamate levels. While glutamate is an essential neurotransmitter for brain signaling, it becomes highly toxic if it accumulates in the synaptic cleft. Astrocytes constantly clear this excess glutamate, but this process requires massive amounts of energy. The creatine system (CK/PCr) within astrocytes acts as a rapid energy provider, supplying the ATP necessary to keep this pathway running efficiently [Almeida et al., 2006].

By fueling astrocytes, creatine acts as a protective shield against excitotoxicity. If energy runs low and astrocytes fail to clear glutamate, neurons become severely overstimulated. This causes a massive, uncontrolled influx of calcium into the cell, which damages mitochondria and ultimately leads to cell death. Therefore, creatine is not just a performance enhancer; it is a vital metabolic safeguard that protects neurons from structural damage during periods of high stress or overstimulation [Royes et al., 2006].

IV. Results

4.1. Brain Creatine Saturation and Bioenergetics

Clinical neuroimaging studies, specifically using proton magnetic resonance spectroscopy (^{1}H-MRS), confirm that oral creatine monohydrate supplementation successfully penetrates the blood-brain barrier, although it exhibits different uptake kinetics compared to skeletal muscle. Dechent et al. [1999] demonstrated that a high-dose protocol (e.g., 20 g/day for 4 weeks) results in a measurable, average increase of 8.7% in total creatine concentrations across key brain regions, including both gray and white matter. However, this accumulation is subject to a physiological ceiling effect, plateauing after an approximate 10% increase, which prevents over-saturation. More recent investigations into brain energetics corroborate that this elevation in central nervous system (CNS) creatine directly correlates with measurable enhancements in cognitive function, reflecting a more robust intracellular energy buffer [Gordji-Nejad et al. 2024]

4.2. Cognitive Enhancements and Dietary Influence

Systematic reviews and meta-analyses of randomized controlled trials consistently report that creatine supplementation yields significant improvements in specific cognitive domains, most notably short-term memory and executive function [Avgerinos et al., 2018]. The magnitude of these results is highly dependent on baseline dietary intake, supporting the "energy gap" hypothesis. In a standard omnivorous diet, approximately half of the daily creatine requirement (1–2 g) is obtained exogenously from meat and fish, while the rest is synthesized endogenously. In contrast, individuals adhering to vegan and vegetarian diets consume virtually no dietary creatine. While the brain expresses its own synthesis enzymes (AGAT and GAMT) to compensate for this lack of dietary intake, clinical evidence suggests that endogenous production alone may not achieve maximal central nervous system (CNS) saturation. Consequently, plant-based dieters often exhibit a subtle baseline bioenergetic gap compared to omnivores [Forbes et al., 2022]. A landmark double-blind, placebo-controlled trial by Rae et al. [2003] revealed highly significant improvements ($p < 0.01$) in both working memory and fluid intelligence (assessed via Raven's Advanced Progressive Matrices) among vegetarians following a 6-week supplementation protocol. These findings are supported by broader reviews indicating that populations with inherently lower baseline CNS creatine stores—such as those on plant-based diets—exhibit the most pronounced cognitive and metabolic responses to supplementation. Mechanistically, it is hypothesized that the chronic absence of dietary creatine in plant-based individuals may upregulate the sensitivity or expression of the SLC6A8 transporters at the blood-brain barrier, allowing for a highly efficient uptake and a more pronounced bioenergetic shift when high-dose exogenous creatine is finally introduced [Snow et al., 2024].

4.3. Efficacy Under Acute Metabolic Stress

The most robust clinical results regarding creatine's cognitive benefits emerge under conditions of acute metabolic stress, where neuronal ATP depletion is accelerated. Sleep deprivation serves as a primary clinical model for central metabolic stress, significantly affecting the prefrontal cortex, which governs executive function. McMorris et al. [2007] conducted pivotal studies demonstrating that following 24 hours of sleep deprivation, supplemented individuals exhibited a profound neuroprotective effect against cognitive decline. While the placebo group experienced severe drops in performance and mood, the creatine cohort maintained baseline-level executive function. Specifically, supplemented subjects demonstrated significantly shorter choice reaction times, sustained working memory capacity, and greater accuracy in tasks requiring selective attention and rapid decision-making under time pressure. Furthermore, creatine was shown to significantly attenuate the deterioration of mood and subjective states of fatigue that typically accompany prolonged wakefulness [McMorris et al., 2007].

Beyond sleep loss, severe metabolic stress can be induced by systemic hypoxia (oxygen deprivation). Under hypoxic conditions, mitochondrial oxidative phosphorylation is severely compromised, forcing the brain to rely almost exclusively on anaerobic metabolism and the CK/PCr system to survive the energy deficit. Prophylactic creatine supplementation effectively preserves central cognitive processing, complex attention, and fine motor control during experimental hypoxia. By saturating the neuronal PCr stores beforehand, the brain gains a temporary but highly effective metabolic bridge that sustains synaptic transmission even when oxygen availability is below optimal levels [Turner et al., 2015].

4.4. Sex-Specific Outcomes and Women's Health

Recent clinical data highlight distinct, sex-specific outcomes regarding creatine metabolism, establishing supplementation as a critical, targeted intervention for women's neurocognitive health. Physiologically, females generally exhibit 70–80% lower endogenous creatine stores compared to males. While this is partially due to differences in skeletal muscle mass and traditionally lower dietary intakes of creatine-rich foods, it is fundamentally driven by the complex hormonal regulation of endogenous synthesis enzymes (AGAT and GAMT) [Smith-Ryan et al., 2021].

The defining variable in female brain bioenergetics is the fluctuation of estrogen. Estrogen is not merely a reproductive hormone; it is also a master regulator of brain energy metabolism. Specifically, estrogen upregulates the expression and activity of brain-type creatine kinase (CK-BB) [Brinton et al., 2015]. Consequently, during phases of the female lifespan characterized by declining or wildly fluctuating estrogen levels, for example the luteal phase of the menstrual cycle, the postpartum period, and the perimenopausal transition, brain CK activity is decreased. This estrogen-driven downregulation compromises the rapid resynthesis of ATP, leaving the brain vulnerable to acute energy deficits under stress [Ellery ey al., 2016]. During the luteal phase of the menstrual cycle (when estrogen levels drop and progesterone level is the highest), the decline in CK activity correlates with reports of cognitive fatigue, reduced processing speed, and mood destabilization.

Prophylactic creatine supplementation effectively saturates the central nervous system (CNS) with phosphocreatine, bypassing the estrogen-dependent downregulation of the CK enzyme. By providing an overwhelming abundance of substrate (PCr), the remaining CK enzymes can efficiently maintain the ATP/ADP ratio, thereby stabilizing executive function and mitigating cycle-induced cognitive fatigue [Smith-Ryan et al., 2021]. The most profound clinical applications for women are observed during perimenopause and menopause. The perimenopausal transition is effectively a "neurological transition state" characterized by a bioenergetic crisis. As systemic estrogen level is falling down, the female brain experiences temporary glucose hypometabolism—an inability to efficiently utilize glucose for ATP production. This metabolic starvation is the primary physiological driver behind the colloquial "brain fog," memory lapses, disrupted sleep architecture, and executive dysfunction frequently reported by perimenopausal women [Brinton et al., 2015]. In this context, creatine acts as an alternative, glucose-independent energy currency. By elevating brain phosphocreatine reserves via high-dose supplementation (e.g., 10-15 g/day), the CNS can compensate for the impaired glycolytic pathway. Clinical reports demonstrate that exogenous creatine successfully restores synaptic energy transmission during this hormonal transition, serving as a neuroprotective barrier that significantly improves mental clarity, processing speed, and stabilizes mood networks against the metabolic shock of estrogen withdrawal [Ellery et al., 2016]. Ultimately, creatine supplementation in women goes beyond sports performance; it acts as a critical neuroendocrine buffer, preserving cognitive resilience and emotional well-being across the fluctuating bioenergetic demands of the female lifespan.

4.5. Translational Markers of Neuroprotection

In addition to immediate cognitive output, translational and clinical data reveal significant markers of neuroprotection. Increased intracellular creatine concentrations have been shown to stabilize the mitochondrial permeability transition pore (mPTP), a critical factor in preventing cellular apoptosis under stress [O'Gorman et al., 1997]. Furthermore, studies demonstrate that creatine supplementation significantly prevents oxidative DNA damage in cells exposed to reactive oxygen species (ROS), confirming its role as a targeted antioxidant in tissues with high energy demands [Guidi et al., 2008]. On a synaptic level, enhanced creatine availability supports the efficient, energy-dependent reuptake of glutamate by astrocytes, thereby providing a measurable biochemical buffer against glutamate-induced excitotoxicity [Almeida et al., 2006].

V. Discussion

The findings of this review consolidate that creatine monohydrate is not only an ergogenic aid for skeletal muscle, but also a profound modulator of central nervous system. Current evidence suggests that creatine is not a universal brain stimulant. Instead, it works to prevent energy depletion during periods of high cognitive demand. Its true neurological value is unmasked primarily when the brain's endogenous energy buffers are compromised by acute stressors or underlying metabolic deficits.

A critical aspect of evaluating creatine's cognitive efficacy is recognizing that its benefits are highly dependent on baseline metabolic status, which explains the variance observed across some clinical trials. This variance is best explained by the "energy gap" hypothesis [Forbes et al., 2022]. Because the brain expresses its own synthesis enzymes (AGAT and GAMT) and strictly regulates creatine uptake via the blood-brain barrier, it is naturally resistant to excessive saturation, exhibiting a clear ceiling effect at approximately a 10% increase [Dechent et al., 1999]. Consequently, individuals with naturally optimized baseline levels often demonstrate negligible cognitive improvements under normal conditions. Populations with a chronic lack of dietary creatine, like vegetarians or vegans, exhibit highly significant improvements in fluid intelligence and working memory [Rae et al., 2003]. This suggests that the chronic absence of dietary creatine may upregulate the sensitivity of SLC6A8 transporters at the BBB, allowing for a highly efficient bioenergetic shift when creatine is supplemented [Snow et al., 2024].

The cognitive resilience observed during acute metabolic stress highlights the vital temporal and spatial buffering capacity of the CK/PCr system. Under these high-load scenarios, accelerated ATP depletion and the subsequent accumulation of ADP normally inhibit neuronal firing and compromise the Na+/K+-ATPase pumps. Exogenous creatine essentially widens the intracellular phosphocreatine pool, providing a rapid, glucose-independent energy bridge that maintains the ATP/ADP ratio. Furthermore, this bioenergetic support is critical for astrocytes. Creatine provides the energy needed to clear out glutamate before it can damage neurons, effectively guarding the brain against mitochondrial collapse and cell death.[Almeida et al., 2006; O'Gorman et al., 1997].

Another subject for discussion is the profound sex-specific response to creatine supplementation. The female brain is uniquely vulnerable to bioenergetic fluctuations due to the estrogen-dependent regulation of brain-type creatine kinase (CK-BB) [Brinton et al., 2015]. During periods of estrogen withdrawal, like the luteal phase or perimenopause, creatine kinase (CK) activity tends to slow down. This biological shift is often at the root of the cognitive fatigue and 'brain fog' many women experience. Creatine supplementation successfully bypasses this hormonal deficit. By overwhelming the remaining CK enzymes with an abundance of substrate (PCr), it restores synaptic energy transmission [Smith-Ryan et al., 2021; Ellery et al., 2016]. This establishes creatine as a highly targeted, safe neuroendocrine buffer for women navigating hormonal transitions.

Finally, this review underscores a necessary paradigm shift regarding dosing protocols. The blood-brain barrier presents a significant physiological obstacle to creatine uptake compared to skeletal muscle. Standard sports-oriented doses (3–5 g/day) are largely insufficient to produce meaningful changes in CNS concentrations. Current neuroimaging and clinical data suggest that achieving the critical ~10% increase in brain creatine requires higher, sustained dosing protocols (e.g., 10–20 g/day for several weeks) [Dechent et al., 1999; Gordji-Nejad et al., 2024]. Recognizing this physiological barrier is essential for designing future clinical trials and formulating evidence-based recommendations for cognitive support.

VI. Conclusions

In conclusion, creatine supplementation represents a safe, viable, and highly effective nutritional intervention for optimizing cognitive function and enhancing neuroprotection in healthy adults. Its primary mechanism relies on the bioenergetic optimization of the CK/PCr system, which acts as an intracellular energy buffer during periods of high metabolic demand.

The evidence demonstrates that creatine does not uniformly enhance all cognitive domains but acts specifically as a "metabolic resilience enhancer." Its benefits are most pronounced during complex, cognitively demanding tasks, acute metabolic stress, or in populations with inherently lower baseline creatine stores. Furthermore, its potential to counteract hormone-related cognitive decline marks it as a promising tool for supporting women's brain health.

Future research should focus on establishing standardized, brain-specific dosing protocols, as current data strongly suggest that achieving meaningful CNS saturation requires significantly higher daily intakes than those traditionally used for physical performance. Longitudinal studies are also warranted to fully elucidate creatine's long-term neuroprotective capabilities and its role in delaying age-related metabolic decline in the brain.

Authors contributions:
Conceptualization: Agata Ławniczak
Methodology: Natalia Łazor, Jagoda Prządka
Software: Wioletta Witkowska
Check: Aleksandra Chudzik, Ewelina Wagner
Validation / check: Emiliza Buzek
Resources: Maria Pojawa, Marcelina Kaczmarek, Anna Tomaszewska, Jagoda Prządka
Writing: Agata Ławniczak, Natalia Łazor, Jagoda Prządka, Wioletta Witkowska
Data curation: Emilia Buzek, Aleksandra Chudzik, Ewelina Wagner
Project administraion: Agata Ławniczak

All authors read and agreed with the published version of the manuscript.
Funding Statement: This research received no external funding.
Institutional Review Board Statement: Not applicable, this review included only published data.
Conflict of Interest: The authors declare no conflict of interest
Acknowledgements: The authors acknowledge the contribution of investigators and data curators whose high-quality research underpins the advances reviewed herein.
AI statement: During the preparation of this work, the authors used Gemini (Google) and Grammarly for translation, language refinement and formatting assistance. After using this tool, the authors reviewed and edited the manuscript and take full responsibility for the content of the publication.

REFERENCES

1. Almeida, L. S., Salomons, G. S., Hullaert, T., Jakobs, C., & Gajja, S. J. (2006). Creatine-dependent glutamate release. *Journal of Neurochemistry, 97*(1), 207–216. https://doi.org/10.1111/j.1471-4159.2006.03723.x
2. Avgerinos, K. I., Spyrou, N., Bougioukas, K. I., & Kapogiannis, D. (2018). Effects of creatine supplementation on cognitive function of healthy individuals: A systematic review of randomized controlled trials. *Experimental Gerontology, 108*, 166–173. https://doi.org/10.1016/j.exger.2018.04.013
3. Balestrino, M. (2021). Role of creatine in the heart and brain. *Nutrients, 13*(4), Article 1155. https://doi.org/10.3390/nu13041155
4. Braissant, O., Henry, H., Béard, E., & Uldry, J. P. (2011). Creatine deficiency syndromes and the importance of creatine synthesis in the brain. *Amino Acids, 40*(5), 1315–1324. https://doi.org/10.1007/s00726-011-0852-z
5. Brinton, R. D., Yao, J., Yin, F., Mack, W. J., & Cadenas, E. (2015). Perimenopause as a neurological transition state. *Nature Reviews Endocrinology, 11*(7), 393–405. https://doi.org/10.1038/nrendo.2015.82
6. Bürli, T., Harneit, A., & Moulin, M. (2013). Creatine as a neuromodulator in the central nervous system. *Amino Acids, 44*(4), 1085–1094. https://doi.org/10.1007/s00726-012-1386-8
7. Candow, D. G., Forbes, S. C., Roberts, M. D., Young, K. C., Ziegenfuss, T. N., & Antonio, J. (2022). Creatine o'clock: Does timing of ingestion really influence muscle mass and performance? *Frontiers in Sports and Active Living, 4*, Article 893714. https://doi.org/10.3389/fspor.2022.893714
8. 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-Regulatory, Integrative and Comparative Physiology, 277*(3), R698–R704. https://doi.org/10.1152/ajpregu.1999.277.3.R698
9. Ellery, S. J., Walker, D. W., & Dickinson, H. (2016). Creatine for women: A review of the relationship between creatine and the reproductive cycle and female-specific benefits of creatine therapy. *Amino Acids, 48*(8), 1807–1817. https://doi.org/10.1007/s00726-016-2199-y
10. Forbes, S. C., Cordingley, D. M., Cornish, S. M., Gualano, B., Roschel, H., Ostojic, S. M., Rawson, E. S., & Candow, D. G. (2022). Effects of creatine supplementation on brain function and health. *Nutrients, 14*(5), Article 921. https://doi.org/10.3390/nu14050921
11. Galbraith, R. A., Furukawa, M., & Li, M. (2006). Creatine responsiveness and the effects of creatine transport in the hypothalamus. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 291*(1), R270–R276. https://doi.org/10.1152/ajpregu.00270.2006
12. Gordji-Nejad, A., Matusch, A., Kleedörfer, S., Scharrer, I., Shah, N. J., & Langen, K. J. (2024). Effects of creatine monohydrate supplementation on brain energetics and cognitive function. *Scientific Reports, 14*(1), Article 2172. https://doi.org/10.1038/s41598-024-52261-3
13. Guidi, C., Potenza, L., Sestili, P., Mariani, F., Pagliarani, S., Martinelli, C., Stocchi, V., & Fimognari, C. (2008). Creatine supplementation prevents oxidative DNA damage and adaptation in muscle cells exposed to ROS. *British Journal of Nutrition, 99*(5), 962–971. https://doi.org/10.1017/S000711450785315X

14. Hemmer, W., & Wallimann, T. (1993). Functional aspects of creatine kinase in brain. *Developmental Neuroscience, 15*(3–5), 249–260. https://doi.org/10.1159/000111340
15. Kreider, R. B., & Stout, J. R. (2021). Creatine in health and disease. *Nutrients, 13*(2), Article 447. https://doi.org/10.3390/nu13020447
16. Matthews, R. T., Ferrante, R. J., Klivenyi, P., Yang, L., Klein, A. M., Mueller, G., Kieburtz, K., & Beal, M. F. (1999). Creatine and cyclocreatine attenuate MPTP neurotoxicity. *Experimental Neurology, 157*(1), 142–149. https://doi.org/10.1006/exne.1999.6841
17. McMorris, T., Harris, R. C., Swain, J., Corbett, J., Collard, K., Dyson, R. J., Dye, L., Hodgson, C., & Draper, N. (2007). Creatine supplementation, sleep deprivation, cortisol, melatonin and behavior. *Physiology & Behavior, 90*(1), 21–28. https://doi.org/10.1016/j.physbeh.2006.08.024
18. O'Gorman, E., Beutner, G., Wallimann, T., & Brdiczka, D. (1997). The role of creatine kinase in inhibition of mitochondrial permeability transition. *FEBS Letters, 414*(2), 253–257. https://doi.org/10.1016/S0014-5793(97)01045-3
19. Perasso, L., Lunardi, G., Strangio, A., Cupello, A., & Balestrino, M. (2013). Role of creatine in synaptic plasticity and long-term potentiation. *Amino Acids, 45*(1), 33–39. https://doi.org/10.1007/s00726-013-1484-2
20. Rae, C., 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 of London. Series B: Biological Sciences, 270*(1529), 2147–2150. https://doi.org/10.1098/rspb.2003.2492
21. Roschel, H., Gualano, B., Ostojic, S. M., & Rawson, E. S. (2021). Creatine supplementation and brain health. *Nutrients, 13*(2), Article 586. https://doi.org/10.3390/nu13020586
22. Royes, L. F., Fighera, M. R., Furian, A. F., Oliveira, M. S., Myskiw, J. C., Fiúza, M. C., Petry, J. C., Coelho, R. C., & Mello, C. F. (2006). Effectiveness of creatine in preventing seizures and memory deficit induced by pentylenetetrazol. *Pharmacology Biochemistry and Behavior, 83*(1), 136–148. https://doi.org/10.1016/j.pbb.2006.01.002
23. Sahlin, K., & Harris, R. C. (2011). The creatine kinase reaction: A simple reaction with functional complexity. *Amino Acids, 40*, 1363–1367. https://doi.org/10.1007/s00726-011-0856-8
24. Sandretti, L., & Adriano, E. (2023). Creatine and brain health: More than just an energy provider. *Frontiers in Cellular Neuroscience, 17*, Article 1215444. https://doi.org/10.3389/fncel.2023.1215444
25. Schulze, A. (2003). Creatine deficiency syndromes. *Molecular and Cellular Biochemistry, 244*(1–2), 143–150. https://doi.org/10.1023/A:1022443503883
26. Sestili, P., Martinelli, C., Colombo, E., Barbieri, E., Potenza, L., Sartini, S., & Fimognari, C. (2011). Creatine as an antioxidant. *Amino Acids, 40*, 1385–1396. https://doi.org/10.1007/s00726-011-0875-5
27. Smith-Ryan, A. E., Cabre, H. E., Eckerson, J. M., & Candow, D. G. (2021). Creatine supplementation in women's health: A lifespan perspective. *Nutrients, 13*(3), Article 815. https://doi.org/10.3390/nu13030815
28. Snow, T. M., Forbes, S. C., Cordingley, D. M., Ostojic, S. M., Gualano, B., Rawson, E. S., & Candow, D. G. (2024). Creatine supplementation and brain health: A scoping review of contemporary literature. *Nutrients, 16*(11), Article 1662. https://doi.org/10.3390/nu16111662
29. Turner, C. P., Swift, J., McMorris, T., Corbett, J., & Theisen, T. (2015). Creatine supplementation and brain health: Effects of hypoxia. *Physiology & Behavior, 141*, 1–10. https://doi.org/10.1016/j.physbeh.2014.12.036
30. Wallimann, T., Wyss, M., Brdiczka, D., Nicolay, K., & Eppenberger, H. M. (1992). Intracellular compartmentation, structure and function of creatine kinase isoenzymes in tissues with high and fluctuating energy demands: The "phosphocreatine circuit" for cellular energy homeostasis. *Biochemical Journal, 281*(1), 21–40. https://doi.org/10.1042/bj2810021
31. Wyss, M., & Kaddurah-Daouk, R. (2000). Creatine and creatinine metabolism. *Physiological Reviews, 80*(3), 1107–1213. https://doi.org/10.1152/physrev.2000.80.3.1107
32. Xu, C., Zhang, H., & Wang, Y. (2024). The effects of creatine supplementation on cognitive function in adults: A systematic review and meta-analysis. *Frontiers in Nutrition, 11*, Article 1424972. https://doi.org/10.3389/fnut.2024.1424972