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Beyond Muscle Energetics: Creatine in Brain Function, Mental Health, and Exercise Performance

Mikołaj Kamela[1], ORCID https://orcid.org/0009-0004-5401-8369

E-mail mikolaj.kamela@gmail.com

[1]Nikolai Pirogov Provincial Specialist Hospital, Łódź, Poland

Michał Kasznicki[2], ORCID https://orcid.org/0009-0006-9205-0858

E-mail michal.kasznicki@stud.umed.lodz.pl

[2]Central Teaching Hospital of the Medical University of Łódź, Łódź, Poland

Małgorzata Czechowska[3], ORCID https://orcid.org/0009-0008-8792-7672

E-mail malgorzata.czechowska@stud.umed.lodz.pl

[3]University Teaching Hospital No. 2, Central Veterans Hospital, Łódź, Poland

Natalia Micek[4], ORCID https://orcid.org/0009-0008-0876-8192

E-mail natalia.micek@stud.umed.lodz.pl

[4]Central Teaching Hospital of the Medical University of Łódź, Łódź, Poland

Alicja Rogozińska[5], ORCID https://orcid.org/0009-0009-1608-3078

E-mail alar2000@wp.pl

[5]Provincial Hospital in Zgierz named after Maria Skłodowska-Curie, Zgierz, Poland

Jakub Łącki[6], ORCID https://orcid.org/0009-0004-0702-6219

E-mail jakublacki@icloud.com

[6]Provincial Hospital in Zgierz named after Maria Skłodowska-Curie, Zgierz, Poland

Emilia Skrzypek[7], ORCID https://orcid.org/0009-0009-0593-3305

E-mail emilia.skrzypek14@gmail.com

[7]Medical University of Łódź, Łódź, Poland

Michał Kalisiak[8], ORCID https://orcid.org/0009-0000-7259-3552

E-mail mckalisiak66@gmail.com

[8]University Teaching Hospital No. 2, Central Veterans Hospital, Łódź, Poland

Karol Jackowiak[9], ORCID https://orcid.org/0009-0007-0335-2940

E-mail jackowiak.kar@gmail.com

[9]Provincial Hospital in Zgierz named after Maria Skłodowska-Curie, Zgierz, Poland

Olgierd Czapiński[10], ORCID https://orcid.org/0009-0007-7894-7201

E-mail olgierd.czapinski@gmail.com

[10]Institute of Dentistry of the Central Teaching Hospital of the Medical University of Łódź, Łódź, Poland

Wiktor Beśka[11], ORCID https://orcid.org/0009-0008-6346-5944

E-mail wiktorb348@gmail.com

[11]Medical University of Łódź, Łódź, Poland

Corresponding Author

Mikołaj Kamela, mikolaj.kamela@gmail.com

Abstract

Background. Creatine is widely recognized for its role in cellular energy metabolism, particularly in skeletal muscle. Increasing evidence indicates that its function extends to the central nervous system, where it may influence cognitive processes, neural stability, and resistance to fatigue.

Aim. The aim of this review is to examine the effects of creatine on brain function, cognitive performance, and exercise-related outcomes, with a focus on mechanisms linking neural and physical performance.

Material and methods. A narrative review of current literature was conducted, including experimental and clinical studies investigating the role of creatine in brain energetics, cognitive function, mental fatigue, and exercise performance.

Results. Available evidence indicates that creatine contributes to the maintenance of stable neural activity under sustained demand. Effects are most evident under conditions of increased cognitive load, sleep deprivation, or prolonged physical effort. While improvements in strength and power performance are consistently reported, effects in endurance and cognitive domains appear more context-dependent and are related to the preservation of signal stability and reduced variability in performance.

Conclusions. Creatine influences both cognitive and physical performance through mechanisms related to the consistency of neural function rather than isolated enhancement of capacity. Its effects are most pronounced in conditions requiring sustained or repeated effort, supporting a unified perspective linking brain function and exercise performance.

Key words: creatine, supplementation, brain, sport, endurance, strength, mental health.

1. Introduction

Creatine supports rapid ATP resynthesis and is well established as a determinant of high-intensity physical performance (1). It is also present in the central nervous system, where it contributes to neuronal energy balance and synaptic function, yet its role in brain processes remains less clearly defined (2).

Cognitive functions such as attention, working memory, and decision-making depend on the ability to sustain coordinated neural activity. Under increased demand, prolonged effort, sleep deprivation, or physical exertion, signaling becomes less consistent, leading to variability in performance and reduced processing efficiency. These constraints extend beyond cognition and influence motor output, linking brain function with physical performance (3).

Evidence indicates that creatine influences performance when maintaining consistent output becomes limiting, rather than through uniform enhancement across conditions (1). This positions creatine as a factor affecting not only muscle energetics but also the interaction between cognitive and motor processes (4).

The aim of this review is to examine the effects of creatine on brain function, cognitive performance, and exercise-related outcomes, with emphasis on mechanisms linking neural stability with performance under sustained or demanding conditions.

2. Research materials and methods

This study is based on a narrative review of literature examining the effects of creatine on brain function, cognitive performance, and exercise-related outcomes. Relevant sources were identified using major scientific databases, including PubMed, Scopus, and Google Scholar.

The selection focused on experimental, clinical, and review studies addressing creatine metabolism in the central nervous system, its role in cognitive processes, and its influence on physical performance. Particular attention was given to conditions involving increased cognitive or energetic demand, such as prolonged effort, fatigue, and sleep deprivation (4).

Sources were selected based on relevance and contribution to the understanding of mechanisms linking neural function with performance. The analysis was qualitative and aimed at integrating findings across cognitive and physical domains.

2.1. AI.

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

3. Research results

3.1. Creatine Metabolism and Transport

Creatine (N-aminoiminomethyl-N-methylglycine) is a naturally occurring nitrogen-containing compound classified within the family of guanidine phosphagens (3).

It is an amino acid derivative synthesized endogenously from glycine and arginine, with the involvement of S-adenosyl methionine (a derivative of methionine), which provides the methyl group necessary for the conversion of guanidinoacetate to creatine. The creatine biosynthesis pathway begins with the formation of guanidinoacetate (GAA) from arginine and glycine, catalyzed by arginine-glycine amidinotransferase (AGAT). Subsequently, GAA undergoes methylation by guanidinoacetate N-methyltransferase (GAMT), with the involvement of S-adenosylmethionine (SAMe), leading to the formation of the final product, creatine (5). The primary organs whose cells express AGAT are the kidneys, pancreas, and liver, with the kidneys exhibiting the highest rate of guanidinoacetate (GAA) synthesis. GAMT expression is highest in the liver, which constitutes the main site of GAA methylation to creatine (6). GAMT is widely expressed in all major brain cell types (neurons, astrocytes, and oligodendrocytes), whereas AGAT is predominantly expressed in neurons and oligodendrocytes within the CNS, indicating that the brain is capable of endogenous creatine synthesis (7).

The maintenance of adequate creatine levels in tissues depends on both endogenous synthesis and exogenous intake from the diet, primarily from meat, fish, and dietary supplements. Approximately 95% of total body creatine is stored in skeletal muscle, while the remainder is distributed among the brain, heart, kidneys, and testes (8,9). The main form of creatine stored in tissues is phosphocreatine (PCr), which is formed by its reversible phosphorylation with inorganic phosphate (Pi). Only a small proportion is stored as free creatine (Cr) (10,11). In skeletal muscle, total creatine content is approximately 120-140 mmol/kg of dry muscle mass, with phosphocreatine accounting for about 60-70% of the total pool, resulting in PCr:Cr ratio of approximately 2:1 (12,13). In the brain, total creatine content is approximately 8–10 mmol/kg, and the PCr:Cr ratio is lower (approximately 1-1.5:1), indicating a more balanced distribution of phosphocreatine (PCr) and free creatine (Cr) compared to skeletal muscle, reflecting differences in energy metabolism between these tissues.

Phosphocreatine is the product of a reversible reaction involving the transfer of a phosphate group from ATP to a molecule of free creatine (Cr), catalyzed by creatine kinase (CK) and occurring primarily in mitochondria. ATP generated during cellular respiration exhibits lower diffusibility compared to phosphocreatine (PCr), highlighting the key role of phosphocreatine in efficient energy transfer between mitochondria and sites of ATP utilization. Phosphocreatine, as a carrier of high-energy phosphate groups, acts as an energy buffer, enabling the rapid resynthesis of ATP at sites of its increased demand. The transfer of a phosphate group from phosphocreatine to ADP is also catalyzed by creatine kinase. This mechanism, referred to as the creatine kinase system, constitutes an essential component of cellular energy homeostasis (11,14).

Creatine is transported via the bloodstream to tissues with high energy demands, where it is taken up by cells. Its cellular uptake is mediated by the creatine transporter SLC6A8, a sodium- and chloride–dependent symporter driven by the transmembrane sodium gradient maintained by Na^+/K^+-ATPase, which is also capable of transporting guanidinoacetate (GAA) with lower affinity. Inhibition of Na^+/K^+-ATPase has been shown to significantly reduce creatine transport, confirming its indirect role in driving creatine uptake (15). The expression of this protein is high in tissues with elevated energy demands, such as skeletal muscle, heart, and brain, highlighting the important role of creatine in cellular energy metabolism (16). Creatine transport into the brain is further restricted by the blood–brain barrier (BBB), limiting its availability within the central nervous system and resulting in a partial reliance of neural tissue on local creatine synthesis (2).

Both creatine and phosphocreatine undergo spontaneous, non-enzymatic and irreversible conversion to creatinine, which is excreted in urine. This process occurs at a relatively constant rate and results in the degradation of approximately 1-2% of the total creatine pool per day, highlighting the need for its continuous replenishment through endogenous synthesis or exogenous intake (17).

3.2. Brain Energy Metabolism and Role of Creatine

Despite accounting for only approximately 2% of total body mass, the brain is responsible for about 20% of resting energy consumption, reflecting its exceptionally high metabolic demand and continuous reliance on ATP due to its limited capacity for energy storage (18). This energy demand is primarily met through the metabolism of glucose via glycolysis and subsequent oxidative phosphorylation (19,20). The high metabolic requirements of the brain arise from the need to maintain membrane potential, support synaptic transmission and sustain the continuous activity of ion pumps, such as Na^+/K^+-ATPase. Consequently, neuronal function is critically dependent on mitochondrial activity and efficient ATP production, making the brain particularly vulnerable to disruptions in energy metabolism, potentially contributing to neurological and psychiatric dysfunction (21,22).

Under conditions of dynamic fluctuations in energy demand, brain energy homeostasis is maintained by the creatine–phosphocreatine (Cr–PCr) system. Phosphocreatine supports the immediate availability of ATP, which is particularly important during synaptic activity and action potential propagation (23,24). This is crucial in regions of intense neuronal signaling, where a rapid energy buffer is required to maintain ion gradients and proper neurotransmission. Additionally, the creatine–phosphocreatine (Cr–PCr) system plays a key role in the spatial distribution of energy within the cell, enabling efficient coupling of mitochondrial ATP production with sites of energy utilization. As a result, it is essential for maintaining neuronal function and supporting cognitive processes (25). Significantly, the efficiency of this system depends not only on its biochemical properties but also on its precise cellular and subcellular localization within the brain.

In this context, both neurons and astrocytes contribute to the maintenance of brain energy homeostasis, although they differ in their metabolic profiles and functional roles (26). Neurons are characterized by particularly high and dynamically fluctuating energy demands, primarily associated with synaptic transmission and the continuous maintenance of ion gradients required for action potential propagation. Due to their limited glycolytic capacity and strong reliance on oxidative phosphorylation, neurons are highly dependent on efficient ATP buffering systems, especially in regions of intense energy utilization such as synapses (20,27).

In contrast, astrocytes primarily perform supportive functions, contributing to the regulation of extracellular ion balance, neurotransmitter recycling, and the provision of metabolic substrates. These cells exhibit a more glycolytic phenotype and play a key role in the astrocyte–neuron lactate shuttle, a mechanism involving the transfer of glycolysis-derived metabolites, such as L-lactate and L-serine, to neurons (26). This process contributes to meeting neuronal energy demands, maintaining redox balance, and modulating neurotransmitter activity.

Although the creatine–phosphocreatine (Cr–PCr) system is present in both cell types, differences in the expression of enzymes involved in creatine synthesis, such as arginine:glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT), as well as in the distribution of the creatine transporter (SLC6A8), indicate cell-type-specific roles and highlight the importance of intercellular cooperation in maintaining brain energy homeostasis (2,28).

3.3. Creatine, Mitochondrial Function, and Neuroprotection

In addition to its function in cellular energy buffering, the creatine–phosphocreatine (Cr–PCr) system is vital within mitochondria. Mitochondrial creatine kinase (mtCK), localized in the intermembrane space, catalyzes the reversible transfer of a phosphate group from ATP to creatine, generating phosphocreatine (29). Tight coupling of this reaction to adenine nucleotide translocase (ANT) and the voltage-dependent anion channel (VDAC) creates a functional microcompartment that enables efficient energy channeling between mitochondria and sites of cytosolic ATP use, highlitghting the role of the creatine–phosphocreatine system in mitochondrial support via ATP/ADP buffering and maintenance of the mitochondrial membrane potential ($\Delta\psi m$) (30,31).

Adequate phosphocreatine availability limits the accumulation of ADP and inorganic phosphate (Pi), thereby reducing the risk of mitochondrial depolarization. This is particularly important under conditions of metabolic stress, where disruptions in $\Delta\Psi m$ can impair ATP synthesis and trigger apoptotic signaling pathways (10). Such dysfunction can impair electron transport chain function, leading to increased electron leakage and subsequent reactive oxygen species (ROS) production (32). By supporting oxidative phosphorylation and stabilizing intracellular energy metabolism, the creatine–phosphocreatine system may reduce electron leakage and limit ROS generation. As a result, improved mitochondrial bioenergetic efficiency reduces oxidative damage to cellular components, including lipids, proteins and mitochondrial DNA, ultimately contributing to the preservation of cellular integrity (33).

The neuroprotective effects of creatine arise from the integration of bioenergetic support and mitochondrial stabilization. By ensuring rapid ATP regeneration, the Cr–PCr system supports the maintenance of ion gradients, thereby reducing the risk of excitotoxic damage associated with excessive glutamate signaling (34). In addition, sustaining cellular energy status limits intracellular calcium overload, a key trigger of mitochondrial dysfunction and opening of the mitochondrial permeability transition pore (mPTP). Through the prevention of mPTP opening and maintenance of mitochondrial integrity, creatine may decrease the release of pro-apoptotic factors, such as cytochrome c, and modulate the activation of apoptotic signaling pathways (35). These mechanisms, together with the regulation of oxidative stress and energy homeostasis, contribute to enhanced neuronal survival and resilience under conditions of metabolic and oxidative challenge.

In vitro studies indicate that creatine supplementation promotes cellular viability during hypoxia (36), primarily by maintaining intracellular ATP-dependent processes, as reflected in decreased mitochondrial depolarization, reduced reactive oxygen species (ROS) formation, and suppression of apoptosis-related signaling pathways. In vivo models further show that creatine administration attenuates neuronal loss and improves functional outcomes following neurological injury and during neurodegenerative processes (37). These effects coincide with sustained mitochondrial integrity, tighter control of intracellular calcium dynamics, and restraint of apoptotic signaling cascades. Collectively, these observations position creatine as a regulator of mitochondrial resilience and neuronal vulnerability in experimental systems.

This becomes especially relevant in Parkinson's disease where mitochondrial dysfunction underlies progressive neuronal loss. By stabilizing ATP availability and modulating oxidative stress, creatine supplementation represents a potential neuroprotective strategy (38).

3.4. Creatine and Mental Health Disorders

Emerging evidence suggests that several psychiatric disorders are associated with disrupted integration of neuronal activity within cortico-limbic circuits, which coordinate emotional processing with executive control. Dysregulation of these networks has been shown to involve altered patterns of synaptic transmission and impaired stability of neuronal signaling across functionally connected regions (39,40). These network-level disturbances reflect underlying bioenergetic constraints.

In this context, the creatine–phosphocreatine (Cr–PCr) system has gained attention as a modulator of synaptic signaling integrity and neuronal network dynamics. By shaping the reliability and temporal precision of neuronal activity, creatine may influence neurotransmission, network excitability, and cognitive function, thereby linking cellular processes with behavioral outcomes.

3.4.1. Depression

Major depressive disorder involves impaired coordination of neuronal activity within cortico-limbic circuits, particularly in the prefrontal cortex and hippocampus. Neuroimaging studies indicate region-specific changes in phosphocreatine levels in these areas, consistent with local bioenergetic limitations affecting neuronal signaling relevant to mood regulation and cognitive processing (41,42). At the synaptic level, depression is characterized by dysregulation of glutamatergic and monoaminergic signaling, accompanied by reduced efficiency of excitatory–inhibitory balance. These alterations may compromise the fidelity and temporal precision of neuronal communication, reducing the ability of neural circuits to sustain coherent patterns of activity (43).

Such disruptions in synaptic signaling place increased demands on processes that sustain rapid neurotransmitter turnover and restoration of ionic gradients during ongoing neuronal activity. Under these conditions, insufficient buffering of local energy fluctuations can amplify variability in synaptic transmission and exacerbate instability of neuronal excitability.

The creatine–phosphocreatine (Cr–PCr) system maintains the efficiency of presynaptic and ion transport mechanisms, where high-frequency turnover is required during repeated firing, enabling more consistent vesicle cycling and faster recovery of ion gradients between successive action potentials. Clinical studies indicate that creatine supplementation may improve treatment response in major depressive disorder, particularly when used as an adjunct to standard antidepressant therapy. Notably, reported effects include accelerated symptom improvement and greater reduction in depressive severity, although findings remain variable across studies (44,45). These outcomes point to a role of creatine in regulating synaptic processes rather than direct neurotransmitter modulation.

3.4.2. Anxiety Disorders

Anxiety disorders feature a shift in cortico-limbic processing toward heightened threat sensitivity, driven by increased responsiveness of the amygdala and insufficient regulatory input from the prefrontal cortex. The imbalance between limbic drive and prefrontal control lowers the threshold for neuronal activation, allowing otherwise transient responses to persist and propagate across interconnected circuits (46–48). This state is reflected in facilitated excitatory transmission and reduced inhibitory gating, which together prolong neuronal firing and impair the termination of stimulus-driven activity. Rather than discrete signaling events, neural responses become temporally extended, increasing the likelihood of recurrent activation within limbic pathways. Such prolongation of neuronal activity places strain on processes responsible for resetting synaptic conditions between successive firing events, including neurotransmitter clearance and restoration of ionic gradients. When these mechanisms fail to keep pace with ongoing activity, residual signaling accumulates, blurring the temporal separation of successive neuronal responses (49,50).

At this stage, the creatine–phosphocreatine (Cr–PCr) system facilitates rapid restoration of synaptic conditions following repeated firing, particularly at presynaptic terminals and ion transport sites. This shortens the duration of individual signaling events and limits the carry-over of residual activity between successive signaling cycles (10). Evidence for creatine supplementation in anxiety disorders remains limited, but available data suggest that its effects in anxiety may involve normalization of activation thresholds and neuronal reactivity.

3.4.3. Schizophrenia and Bipolar Disorder

Schizophrenia and bipolar disorder represent distinct clinical entities that share disruptions in coordination between large-scale brain networks involved in salience detection, cognitive control, and internal mentation. Impaired integration between the prefrontal cortex and subcortical structures, including the striatum, leads to aberrant assignment of salience to internal and external stimuli, contributing to disorganized thought processes in schizophrenia and dysregulated mood states in bipolar disorder (51,52). In schizophrenia, dysregulated dopaminergic signaling and altered interactions between excitatory and inhibitory pathways lead to inappropriate amplification of internally generated signals and reduced discrimination between relevant and irrelevant stimuli. In contrast, bipolar disorder is characterized by fluctuations in synaptic activity across mood states, reflecting impaired regulation of network excitability and instability in transitions between internally and externally oriented processing (53,54).

As a consequence, the fidelity of information processing across distributed networks becomes compromised. In schizophrenia, internally generated representations gain disproportionate influence over perception and cognition, weakening the alignment between sensory input and interpretative frameworks. A different pattern is observed in bipolar disorder, where variability in network engagement, disrupts the consistency of cognitive and emotional responses and leads to fluctuations in how stimuli are evaluated and acted upon (53).

Efficient coordination across distributed networks requires rapid adjustments in synaptic activity during changing cognitive demands. The creatine–phosphocreatine (Cr–PCr) system supports these mechanisms in circuits undergoing frequent transitions between functional states, particularly those linking prefrontal and subcortical regions. This enables more precise alignment of activity across interconnected networks and reduces inappropriate persistence or disengagement of circuit-level responses.

Available studies on creatine supplementation in schizophrenia and bipolar disorder remain limited and heterogeneous (55,56). Reported effects vary across studies and clinical contexts, with no consistent impact on core symptoms. This variability likely reflects the complexity of network-level disturbances underlying these conditions and the absence of a single dominant mechanism that can be uniformly targeted.

3.5. Creatine Supplementation and Brain Function

The effectiveness of creatine intake in the central nervous system is constrained by its transport into the brain. Unlike skeletal muscle, where creatine uptake is relatively efficient, brain availability depends on passage across the blood–brain barrier via the creatine transporter (SLC6A8). Transport across this barrier is slow and tightly regulated, resulting in gradual and often modest increases in brain creatine levels following supplementation. Changes in neural function are therefore less immediate and may depend on sustained intake, particularly under conditions of limited endogenous creatine availability or increased metabolic demand (57,58).

Typical supplementation strategies involve either a loading phase of approximately 20 g/day for 5–7 days followed by a maintenance dose of 3–5 g/day, or continuous supplementation at 3–5 g/day without loading. Higher initial dosing accelerates creatine accumulation in peripheral tissues, but its impact on brain creatine levels appears less pronounced (59). Continuous supplementation at moderate doses results in slower but more stable increases, which may be more relevant for central nervous system effects. The time required to achieve measurable changes in brain creatine content is longer than in skeletal muscle, often extending over several weeks of consistent intake.

Creatine-related changes in brain function vary depending on baseline creatine availability and individual physiological characteristics. Individuals with lower endogenous creatine levels, particularly those adhering to vegetarian or vegan diets, may exhibit more pronounced effects (60). Sex, age, metabolic status, and overall physiological stress also influence outcomes, with greater reactions often observed under conditions of increased cognitive or energetic demand. These factors contribute to variability in response and may explain inconsistencies across studies examining cognitive and neuropsychiatric effects.

Creatine supplementation is generally well tolerated across a wide range of doses and durations. Reported adverse effects are typically mild and most often include gastrointestinal discomfort and transient peripheral fluid retention (61). Current evidence does not support an increased risk of renal dysfunction in healthy individuals, although caution is warranted in those with pre-existing kidney disease. Long-term studies indicate a favorable safety profile, with no consistent evidence of clinically significant adverse outcomes under standard supplementation protocols (62,63).

3.6. Creatine and Exercise Performance

Creatine is widely recognized for its role in enhancing exercise performance, particularly in high-intensity, short-duration activities. While its effects on skeletal muscle are well established, increasing attention has been directed toward its influence on central processes contributing to performance under conditions of fatigue. Physical exertion depends not only on muscular output but also on sustained neural drive and cognitive control, which may be affected by changes in brain energetics and signaling stability. Peripheral effects of creatine support force production and repeated high-intensity efforts, whereas central effects relate to the maintenance of neural activation during prolonged or demanding activity. Performance decline therefore reflects not only limitations within muscle but also reduced efficiency of central motor drive, highlighting a potential role for creatine in sustaining neural output during demanding conditions (64,65).

3.6.1. Peripheral vs Central Effects

Exercise performance requires the integration of peripheral muscle function and central neural drive. Peripheral mechanisms determine force production capacity and energy turnover within muscle, whereas central processes regulate motor unit recruitment, coordination, and the maintenance of voluntary effort. During sustained or high-intensity activity, the capacity of the central nervous system to generate consistent output declines, leading to reductions in motor drive that are not fully explained by muscular limitations alone (64,66).

The effects of creatine are most apparent in high-intensity, repeated efforts, where rapid energy turnover limits force output. Less attention has been given to its influence on central processes, despite their contribution to performance under sustained or demanding conditions. As exertion continues, neural output becomes less consistent, and variability in motor signaling begins to affect coordination and voluntary drive. Under these conditions, creatine may help stabilize activity within motor pathways, supporting more reliable motor unit recruitment and preserving coordination as central drive declines (8).

3.6.2. Creatine and Central Fatigue

Central fatigue limits the ability to sustain voluntary drive during ongoing physical effort. The decline does not arise solely from peripheral constraints but reflects reduced precision and stability of signaling within motor pathways (67). With increasing effort, motor output becomes less consistent, coordination deteriorates, and effort must be reinforced to maintain performance. Force production alone no longer determines performance; its continuity and control become limiting factors. Under these conditions, stability of neural output becomes critical. Reduced variability in motor signaling supports more consistent recruitment patterns and limits fluctuations in performance when effort is sustained or repeatedly reinitiated. This provides a mechanistic basis for performance effects that extend beyond peripheral muscle function.

The decline in central drive does not follow a purely linear trajectory. Periods of stable output are interrupted by brief drops in force and coordination, requiring repeated re-engagement of effort to maintain performance. This variability becomes more pronounced over time, reflecting an increasing mismatch between intended and executed motor output. In this context, even small fluctuations in neural signaling can translate into measurable changes in performance, particularly when precision and timing are critical (68).

3.6.3. Cognitive Performance During Exercise

Cognitive demands do not diminish during physical exertion; in many settings they intensify. Decision-making, attentional focus, and response selection must be maintained despite progressive strain on neural systems. As a result, performance errors often arise not from insufficient force but from delayed or inaccurate execution of otherwise appropriate actions. Small disruptions in timing or attentional control can alter outcomes, particularly in tasks requiring rapid adjustments to changing sensory input (69,70). Reaction speed slows, but variability between responses becomes equally relevant, increasing the likelihood of misjudgment or mistimed actions. Maintaining stable neural output under sustained effort therefore influences not only physical execution but also the precision and reliability of behavior in time-sensitive contexts.

3.6.4. Endurance vs Strength Context

Creatine shows consistent benefits in strength and power tasks, where repeated high-intensity output is required. In contrast, effects in endurance settings are less predictable. Performance in these contexts relies on pacing and efficiency rather than peak force, making outcomes less directly tied to short-term output capacity (71). Limitations develop progressively and reflect interacting central and peripheral constraints. Instead of clear increases in output, changes are more often expressed as improved stability across prolonged effort and reduced variability in performance. This becomes relevant in tasks requiring continuous adjustment, where small inconsistencies can accumulate into measurable performance differences.

3.7. Bridging Mental Health and Exercise Performance

Mental health and exercise performance are typically considered separately, yet both rely on the capacity to sustain coordinated neural activity under ongoing demand. In psychiatric conditions, instability of signaling disrupts cognitive and emotional regulation; in physical performance, similar instability reduces motor drive, degrades coordination, and increases variability of output. The manifestations differ, but the underlying constraint remains the same: maintaining consistent neural output over time (72).

This overlap shifts attention away from isolated neurotransmitter systems or single performance metrics toward the reliability of neural signaling itself. Effects observed across domains may therefore reflect improved continuity of neural activity rather than direct modulation of specific pathways. Such a perspective provides a functional link between mental health and performance.

Prolonged cognitive effort, physical exertion, or their combination expose limitations in the consistency of signaling, leading to variability in both behavioral and motor responses. In such contexts, performance is shaped less by maximal capacity and more by the ability to preserve reliable output despite accumulating strain, which places greater emphasis on mechanisms that support continuity of function across time rather than peak efficiency at a single point. Creatine illustrates an intervention that influences the reliability of neural function under sustained demand. Effects emerge when maintaining consistent output becomes limiting, rather than as isolated gains in strength or cognition (4).

Viewing mental health and exercise performance through a shared functional lens highlights the importance of maintaining stable neural activity over time. Rather than focusing on separate domains, this perspective underlines common constraints that shape both behavior and performance. Approaches that improve the consistency of neural function can extend across contexts where cognitive and physical demands intersect.

4. Discussion

The findings converge on the role of stable neural function as a limiting factor in both cognitive and physical performance under increased demand. Performance decline reflects not only reduced capacity but also growing variability in neural signaling, affecting both behavior and motor output (73,74).

Within this framework, creatine appears to influence performance when maintaining consistent output becomes challenging, rather than producing uniform improvements across conditions. This may account for more pronounced effects under prolonged effort, sleep deprivation, or repeated high-intensity activity (75).

Variability in outcomes across studies likely reflects differences in baseline physiology, task demands, and study design, particularly in cognitive and endurance contexts where effects are less consistent than in strength-based performance.

5. Conclusions

Creatine affects both cognitive and physical performance through mechanisms linked to the stability of neural function under demanding conditions. Effects emerge when maintaining consistent output becomes limiting, rather than as uniform improvements across contexts (76).

This links brain function and exercise performance through shared constraints on neural activity, emphasizing reliability and coordination over time. Further work should define the conditions and populations in which these effects are most relevant.

Disclossure

The authors declares no competing interests.

Author Contributions

Conceptualization, M. Kamela, and O. Czapiński; methodology, M. Kamela, M. Kalisiak, and M. Czechowska; software, M. Kamela, N. Micek, J. Łącki, and E. Skrzypek; check, K. Jackowiak, A. Rogozińska, and M. Kasznicki; formal analysis, M. Kasznicki, and M. Kamela; investigation, M. Czechowska, and O. Czapiński; resources, M. Nicek, E. Skrzypek, and W. Beśka; data curation, W. Beśka, K. Jackowiak, and M. Kamela; writing - rough preparation, M. Kamela, K. Jackowiak, and A. Rogozińska; writing - review and editing, J. Łącki, and W. Beśka; visualization, E. Skrzypek, M. Kamela, and M. Czechowska; supervision, M. Kamela; project administration, M. Kamela;

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The authors declares no conflict of interest.

Declaration of the use of generative AI

In preparing this work, the author used ChatGPT (OpenAI) for linguistic refinement and improvement of clarity and style. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the final version of the manuscript.

References

1. Sahlin K, Tonkonogi M, Söderlund K. Energy supply and muscle fatigue in humans. Acta Physiologica Scandinavica. 1998 Feb;162(3):261–6. doi:10.1046/j.1365-201X.1998.0298f.x

2. Braissant O, Henry H, Loup M, Eilers B, Bachmann C. Endogenous synthesis and transport of creatine in the rat brain: an in situ hybridization study. Molecular Brain Research. 2001 Jan;86(1–2):193–201. doi:10.1016/S0169-328X(00)00269-2

3. Ellington WR. Evolution and Physiological Roles of Phosphagen Systems. Annu Rev Physiol. 2001 Mar;63(1):289–325. doi:10.1146/annurev.physiol.63.1.289

4. Dolan E, Gualano B, Rawson ES. Beyond muscle: the effects of creatine supplementation on brain creatine, cognitive processing, and traumatic brain injury. European Journal of Sport Science. 2019 Feb;19(1):1–14. doi:10.1080/17461391.2018.1500644

5. Da Silva RP, Nissim I, Brosnan ME, Brosnan JT. Creatine synthesis: hepatic metabolism of guanidinoacetate and creatine in the rat in vitro and in vivo. American Journal of Physiology-Endocrinology and Metabolism. 2009 Feb;296(2):E256–61. doi:10.1152/ajpendo.90547.2008

6. Da Silva RP, Clow K, Brosnan JT, Brosnan ME. Synthesis of guanidinoacetate and creatine from amino acids by rat pancreas. Br J Nutr. 2014 Feb 28;111(4):571–7. doi:10.1017/S0007114513003012

7. Sarter M, Givens B, Bruno JP. The cognitive neuroscience of sustained attention: where top-down meets bottom-up. Brain Research Reviews. 2001 Apr;35(2):146–60. doi:10.1016/S0165-0173(01)00044-3

8. Demant T, Rhodes E. Effects of Creatine Supplementation on Exercise Performance: Sports Medicine. 1999;28(1):49–60. doi:10.2165/00007256-199928010-00005

9. Balsom PD, Söderlund K, Ekblom B. Creatine in Humans with Special Reference to Creatine Supplementation: Sports Medicine. 1994 Oct;18(4):268–80. doi:10.2165/00007256-199418040-00005

10. Wallimann T, Tokarska-Schlattner M, Schlattner U. The creatine kinase system and pleiotropic effects of creatine. Amino Acids. 2011 May;40(5):1271–96. doi:10.1007/s00726-011-0877-3

11. Meyer RA, Sweeney HL, Kushmerick MJ. A simple analysis of the ‘phosphocreatine shuttle’. American Journal of Physiology-Cell Physiology. 1984 May 1;246(5):C365–77. doi:10.1152/ajpcell.1984.246.5.C365

12. Balsom PD, Söderlund K, Sjödin B, Ekblom B. Skeletal muscle metabolism during short duration high-intensity exercise: influence of creatine supplementation. Acta Physiologica Scandinavica. 1995 Jul;154(3):303–10. doi:10.1111/j.1748-1716.1995.tb09914.x

13. Kushmerick MJ, Moerland TS, Wiseman RW. Mammalian skeletal muscle fibers distinguished by contents of phosphocreatine, ATP, and Pi. Proc Natl Acad Sci USA. 1992 Aug 15;89(16):7521–5. doi:10.1073/pnas.89.16.7521

14. Jacobus WE, Lehninger AL. Creatine Kinase of Rat Heart Mitochondria. Journal of Biological Chemistry. 1973 Jul;248(13):4803–10. doi:10.1016/S0021-9258(19)43737-X

15. Peral MJ, García-Delgado M, Calonge ML, Durán JM, De La Horra MC, Wallimann T, et al. Human, rat and chicken small intestinal Na^+ -Cl^- -creatine transporter: functional, molecular characterization and localization. The Journal of Physiology. 2002 Nov;545(1):133–44. doi:10.1113/jphysiol.2002.026377

16. Saltarelli MD, Bauman AL, Moore KR, Bradley CC, Blakely RD. Expression of the Rat Brain Creatine Transporter in situ and in Transfected HeLa Cells. Dev Neurosci. 2009 Aug 24;524–34. doi:10.1159/000111450

17. Spencer K. Analytical Reviews in Clinical Biochemistry: The Estimation of Creatinine. Ann Clin Biochem. 1986 Jan;23(1):1–25. doi:10.1177/000456328602300101

18. Shulman RG, Rothman DL, Behar KL, Hyder F. Energetic basis of brain activity: implications for neuroimaging. Trends in Neurosciences. 2004 Aug;27(8):489–95. doi:10.1016/j.tins.2004.06.005

19. Ivanov AI, Malkov AE, Waseem T, Mukhtarov M, Buldakova S, Gubkina O, et al. Glycolysis and Oxidative Phosphorylation in Neurons and Astrocytes during Network Activity in Hippocampal Slices. J Cereb Blood Flow Metab. 2014 Mar;34(3):397–407. doi:10.1038/jcbfm.2013.222

20. Hall CN, Klein-Flugge MC, Howarth C, Attwell D. Oxidative Phosphorylation, Not Glycolysis, Powers Presynaptic and Postsynaptic Mechanisms Underlying Brain Information Processing. Journal of Neuroscience. 2012 Jun 27;32(26):8940–51. doi:10.1523/JNEUROSCI.0026-12.2012

21. Erecińska M, Dagani F. Relationships between the neuronal sodium/potassium pump and energy metabolism. Effects of K+, Na+, and adenosine triphosphate in isolated brain synaptosomes. The Journal of general physiology. 1990 Apr 1;95(4):591–616. doi:10.1085/jgp.95.4.591

22. Bertorello AM, Hopfield JF, Aperia A, Greengard P. Inhibition by dopamine of (Na+ + K+)ATPase activity in neostriatal neurons through D1 and D2 dopamine receptor synergism. Nature. 1990 Sep 27;347(6291):386–8. doi:10.1038/347386a0

23. Tachikawa M, Fukaya M, Terasaki T, Ohtsuki S, Watanabe M. Distinct cellular expressions of creatine synthetic enzyme GAMT and creatine kinases uCK-Mi and CK-B suggest a novel neuron–glial relationship for brain energy homeostasis. Eur J of Neuroscience. 2004 Jul;20(1):144–60. doi:10.1111/j.1460-9568.2004.03478.x

24. Rangaraju V, Calloway N, Ryan TA. Activity-Driven Local ATP Synthesis Is Required for Synaptic Function. Cell. 2014 Feb;156(4):825–35. doi:10.1016/j.cell.2013.12.042

25. Andres RH, Ducray AD, Schlattner U, Wallimann T, Widmer HR. Functions and effects of creatine in the central nervous system. Brain Research Bulletin. 2008 Jul;76(4):329–43. doi:10.1016/j.brainresbull.2008.02.035

26. Bonvento G, Bolaños JP. Astrocyte-neuron metabolic cooperation shapes brain activity. Cell Metabolism. 2021 Aug;33(8):1546–64. doi:10.1016/j.cmet.2021.07.006

27. Jang S, Nelson JC, Bend EG, Rodríguez-Laureano L, Tueros FG, Cartagenova L, et al. Glycolytic enzymes localize to synapses under energy stress to support synaptic function [Internet]. Cell Biology; 2016 [cited 2026 Apr 26]. Available from: http://biorxiv.org/lookup/doi/10.1101/042002 doi:10.1101/042002

28. Braissant O, Henry H. AGAT, GAMT and SLC6A8 distribution in the central nervous system, in relation to creatine deficiency syndromes: A review. J of Inher Metab Disea. 2008 Apr;31(2):230–9. doi:10.1007/s10545-008-0826-9

29. Miller K, Sharer K, Suhan J, Koretsky AP. Expression of functional mitochondrial creatine kinase in liver of transgenic mice. American Journal of Physiology-Cell Physiology. 1997 Apr 1;272(4):C1193–202. doi:10.1152/ajpcell.1997.272.4.C1193

30. Dolder M, Wendt S, Wallimann T. Mitochondrial Creatine Kinase in Contact Sites: Interaction with Porin and Adenine Nucleotide Translocase, Role in Permeability Transition and Sensitivity to Oxidative Damage. Biol Signals Recept. 2001;10(1–2):93–111. doi:10.1159/000046878

31. Wallimann T, Dolder M, Schlattner U, Eder M, Hornemann T, O'Gorman E, et al. Some new aspects of creatine kinase (CK): compartmentation, structure, function and regulation for cellular and mitochondrial bioenergetics and physiology. BioFactors. 1998 Jan;8(3–4):229–34. doi:10.1002/biof.5520080310

32. Ricci JE, Gottlieb RA, Green DR. Caspase-mediated loss of mitochondrial function and generation of reactive oxygen species during apoptosis. The Journal of Cell Biology. 2003 Jan 6;160(1):65–75. doi:10.1083/jcb.200208089

33. Kowaltowski AJ, Vercesi AE. Mitochondrial damage induced by conditions of oxidative stress. Free Radical Biology and Medicine. 1999 Feb;26(3–4):463–71. doi:10.1016/S0891-5849(98)00216-0

34. Nicholls DG, Budd SL, Castilho RF, Ward MW. Glutamate Excitotoxicity and Neuronal Energy Metabolism. Annals of the New York Academy of Sciences. 1999 Nov;893(1):1–12. doi:10.1111/j.1749-6632.1999.tb07813.x

35. Brookes PS, Yoon Y, Robotham JL, Anders MW, Sheu SS. Calcium, ATP, and ROS: a mitochondrial love-hate triangle. American Journal of Physiology-Cell Physiology. 2004 Oct;287(4):C817–33. doi:10.1152/ajpcell.00139.2004

36. Balestrino M, Rebaudo R, Lunardi G. Exogenous creatine delays anoxic depolarization and protects from hypoxic damage: dose–effect relationship. Brain Research. 1999 Jan;816(1):124–30. doi:10.1016/S0006-8993(98)01131-7

37. Beal MF. Neuroprotective effects of creatine. Amino Acids. 2011 May;40(5):1305–13. doi:10.1007/s00726-011-0851-0

38. Attia A, Ahmed H, Gadelkarim M, Morsi M, Awad K, Elnenny M, et al. Meta-Analysis of Creatine for Neuroprotection Against Parkinson’s Disease. CNSNDDT. 2017 Feb 15;16(2):169–75. doi:10.2174/1871527315666161104161855

39. McTeague LM, Rosenberg BM, Lopez JW, Carreon DM, Huemer J, Jiang Y, et al. Identification of Common Neural Circuit Disruptions in Emotional Processing Across Psychiatric Disorders. AJP. 2020 May 1;177(5):411–21. doi:10.1176/appi.ajp.2019.18111271

40. Kapogiannis D, Mattson MP. Disrupted energy metabolism and neuronal circuit dysfunction in cognitive impairment and Alzheimer’s disease. The Lancet Neurology. 2011 Feb;10(2):187–98. doi:10.1016/S1474-4422(10)70277-5

41. Harper DG, Jensen JE, Ravichandran C, Perlis RH, Fava M, Renshaw PF, et al. Tissue Type-Specific Bioenergetic Abnormalities in Adults with Major Depression. Neuropsychopharmacol. 2017 Mar;42(4):876–85. doi:10.1038/npp.2016.180

42. Kato T, Takahashi S, Shioiri T, Inubushi T. Brain phosphorous metabolism in depressive disorders detected by phosphorus-31 magnetic resonance spectroscopy. Journal of Affective Disorders. 1992 Dec;26(4):223–30. doi:10.1016/0165-0327(92)90099-R

43. Lener MS, Niciu MJ, Ballard ED, Park M, Park LT, Nugent AC, et al. Glutamate and Gamma-Aminobutyric Acid Systems in the Pathophysiology of Major Depression and Antidepressant Response to Ketamine. Biological Psychiatry. 2017 May;81(10):886–97. doi:10.1016/j.biopsych.2016.05.005

44. Lyoo IK, Yoon S, Kim TS, Hwang J, Kim JE, Won W, et al. A Randomized, Double-Blind Placebo-Controlled Trial of Oral Creatine Monohydrate Augmentation for Enhanced Response to a Selective Serotonin Reuptake Inhibitor in Women With Major Depressive Disorder. AJP. 2012 Sep;169(9):937–45. doi:10.1176/appi.ajp.2012.12010009

45. Kondo DG, Sung YH, Hellem TL, Fiedler KK, Shi X, Jeong EK, et al. Open-label adjunctive creatine for female adolescents with SSRI-resistant major depressive disorder: A 31-phosphorus magnetic resonance spectroscopy study. Journal of Affective Disorders. 2011 Dec;135(1–3):354–61. doi:10.1016/j.jad.2011.07.010

46. Hultman R, Mague SD, Li Q, Katz BM, Michel N, Lin L, et al. Dysregulation of Prefrontal Cortex-Mediated Slow-Evolving Limbic Dynamics Drives Stress-Induced Emotional Pathology. Neuron. 2016 Jul;91(2):439–52. doi:10.1016/j.neuron.2016.05.038

47. Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HMC, et al. Amygdala and Ventrolateral Prefrontal Cortex Activation to Masked Angry Faces in Children and Adolescents With Generalized Anxiety Disorder. Arch Gen Psychiatry. 2008 May 1;65(5):568. doi:10.1001/archpsyc.65.5.568

48. Kenwood MM, Kalin NH, Barbas H. The prefrontal cortex, pathological anxiety, and anxiety disorders. Neuropsychopharmacol. 2022 Jan;47(1):260–75. doi:10.1038/s41386-021-01109-z

49. Davis GW, Müller M. Homeostatic Control of Presynaptic Neurotransmitter Release. Annu Rev Physiol. 2015 Feb 10;77(1):251–70. doi:10.1146/annurev-physiol-021014-071740

50. Contreras SA, Schleimer JH, Gulledge AT, Schreiber S. Activity-mediated accumulation of potassium induces a switch in firing pattern and neuronal excitability type. Rubin J, editor. PLoS Comput Biol. 2021 May 27;17(5):e1008510. doi:10.1371/journal.pcbi.1008510

51. Mamah D, Barch DM, Repovš G. Resting state functional connectivity of five neural networks in bipolar disorder and schizophrenia. Journal of Affective Disorders. 2013 Sep;150(2):601–9. doi:10.1016/j.jad.2013.01.051

52. Calhoun VD, Sui J, Kiehl K, Turner J, Allen E, Pearlson G. Exploring the Psychosis Functional Connectome: Aberrant Intrinsic Networks in Schizophrenia and Bipolar Disorder. Front Psychiatry. 2012;2. doi:10.3389/fpsyt.2011.00075

53. Heinz A, Schlagenhauf F. Dopaminergic Dysfunction in Schizophrenia: Salience Attribution Revisited. Schizophrenia Bulletin. 2010 May 1;36(3):472–85. doi:10.1093/schbul/sbq031

54. Schloesser RJ, Huang J, Klein PS, Manji HK. Cellular Plasticity Cascades in the Pathophysiology and Treatment of Bipolar Disorder. Neuropsychopharmacol. 2008 Jan;33(1):110–33. doi:10.1038/sj.npp.1301575

55. Kraguljac NV, Reid M, White D, Jones R, Den Hollander J, Lowman D, et al. Neurometabolites in schizophrenia and bipolar disorder — A systematic review and meta-analysis. Psychiatry Research: Neuroimaging. 2012 Aug;203(2–3):111–25. doi:10.1016/j.pscychresns.2012.02.003

56. Toniolo RA, Fernandes FDBF, Silva M, Dias RDS, Lafer B. Cognitive effects of creatine monohydrate adjunctive therapy in patients with bipolar depression: Results from a randomized, double-blind, placebo-controlled trial. Journal of Affective Disorders. 2017 Dec;224:69–75. doi:10.1016/j.jad.2016.11.029

57. Ohtsuki S, Tachikawa M, Takanaga H, Shimizu H, Watanabe M, Hosoya K ichi, et al. The Blood–Brain Barrier Creatine Transporter is a Major Pathway for Supplying Creatine to the Brain. J Cereb Blood Flow Metab. 2002 Nov;22(11):1327–35. doi:10.1097/01.WCB.0000033966.83623.7D

58. Braissant O. Creatine and guanidinoacetate transport at blood-brain and blood-cerebrospinal fluid barriers. J of Inher Metab Disea. 2012 Jul;35(4):655–64. doi:10.1007/s10545-011-9433-2

59. Bemben MG, Lamont HS. Creatine Supplementation and Exercise Performance: Recent Findings. Sports Medicine. 2005;35(2):107–25. doi:10.2165/00007256-200535020-00002

60. Benton D, Donohoe R. The influence of creatine supplementation on the cognitive functioning of vegetarians and omnivores. Br J Nutr. 2011 Apr 14;105(7):1100–5. doi:10.1017/S0007114510004733

61. Groeneveld GJ, Beijer C, Veldink JH, Kalmijn S, Wokke JHJ, Van Den Berg LH. Few Adverse Effects of Long-Term Creatine Supplementation in a Placebo-Controlled Trial. Int J Sports Med. 2005 May;26(4):307–13. doi:10.1055/s-2004-817917

62. Yoshizumi WM, Tsourounis C. Effects of Creatine Supplementation on Renal Function. Journal of Herbal Pharmacotherapy. 2004 Jan;4(1):1–7. doi:10.1080/J157v04n01_01

63. Kim HJ, Kim CK, Carpentier A, Poortmans JR. Studies on the safety of creatine supplementation. Amino Acids. 2011 May;40(5):1409–18. doi:10.1007/s00726-011-0878-2

64. Amann M. Central and Peripheral Fatigue: Interaction during Cycling Exercise in Humans. Medicine & Science in Sports & Exercise. 2011 Nov;43(11):2039–45. doi:10.1249/MSS.0b013e31821f59ab

65. Mujika I, Padilla S. Creatine Supplementation as an Ergogenic Aid for Sports Performance in Highly Trained Athletes: A Critical Review. Int J Sports Med. 1997 Oct;18(07):491–6. doi:10.1055/s-2007-972670

66. Gandevia SC, Allen GM, Butler JE, Taylor JL. Supraspinal factors in human muscle fatigue: evidence for suboptimal output from the motor cortex. The Journal of Physiology. 1996 Jan 15;490(2):529–36. doi:10.1113/jphysiol.1996.sp021164

67. Taylor JL, Gandevia SC. A comparison of central aspects of fatigue in submaximal and maximal voluntary contractions. Journal of Applied Physiology. 2008 Feb;104(2):542–50. doi:10.1152/japplphysiol.01053.2007

68. Churchland MM, Afshar A, Shenoy KV. A Central Source of Movement Variability. Neuron. 2006 Dec;52(6):1085–96. doi:10.1016/j.neuron.2006.10.034

69. Féry YA, Ferry A, Hofe AV, Rieu M. Effect of Physical Exhaustion on Cognitive Functioning. Percept Mot Skills. 1997 Feb;84(1):291–8. doi:10.2466/pms.1997.84.1.291

70. Brisswalter J, Collardeau M, Ren?? A. Effects of Acute Physical Exercise Characteristics on Cognitive Performance: Sports Medicine. 2002;32(9):555–66. doi:10.2165/00007256-200232090-00002

71. Wax B, Kerksick CM, Jagim AR, Mayo JJ, Lyons BC, Kreider RB. Creatine for Exercise and Sports Performance, with Recovery Considerations for Healthy Populations. Nutrients. 2021 Jun 2;13(6):1915. doi:10.3390/nu13061915

72. Strauss E, Macdonald SWS, Hunter M, Moll A, Hultsch DF. Intraindividual variability in cognitive performance in three groups of older adults: Cross-domain links to physical status and self-perceived affect and beliefs. J Int Neuropsychol Soc. 2002 Nov;8(7):893–906. doi:10.1017/S1355617702870035

73. Waschke L, Kloosterman NA, Obleser J, Garrett DD. Behavior needs neural variability. Neuron. 2021 Mar;109(5):751–66. doi:10.1016/j.neuron.2021.01.023

74. Vanden Noven ML, Pereira HM, Yoon T, Stevens AA, Nielson KA, Hunter SK. Motor Variability during Sustained Contractions Increases with Cognitive Demand in Older Adults. Front Aging Neurosci. 2014 May 22;6. doi:10.3389/fnagi.2014.00097

75. McMorris T, Harris RC, Howard AN, Langridge G, Hall B, Corbett J, et al. Creatine supplementation, sleep deprivation, cortisol, melatonin and behavior. Physiology & Behavior. 2007 Jan;90(1):21–8. doi:10.1016/j.physbeh.2006.08.024

76. Avgerinos KI, Spyrou N, Bougioukas KI, Kapogiannis D. Effects of creatine supplementation on cognitive function of healthy individuals: A systematic review of randomized controlled trials. Experimental Gerontology. 2018 Jul;108:166–73. doi:10.1016/j.exger.2018.04.013