A Report on "Single Dose Creatine Improves Cognitive Performance and Induces Changes in Cerebral High Energy Phosphates During Sleep Deprivation" by Gordji-Nejad et al. (2024)

Reviewer 2

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> I am wiser than this person; for it is likely that neither of us knows anything fine and good, but he thinks he knows something when he does not know it, whereas I, just as I do not know, do not think I know, either. I seem, then, to be wiser than him in this small way, at least: that what I do not know, I do not think I know, either.
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> Plato, *The Apology of Socrates*, 21d

> To err is human. All human knowledge is fallible and therefore uncertain. It follows that we must distinguish sharply between truth and certainty. That to err is human means not only that we must constantly struggle against error, but also that, even when we have taken the greatest care, we cannot be completely certain that we have not made a mistake.
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> Karl Popper, 'Knowledge and the Shaping of Reality'

Overview

Citation: Gordji-Nejad, A., Matusch, A., Kleedörfer, S., Patel, H. J., Drzezga, A., Elmenhorst, D., Binkofski, F., & Bauer, A. (2024). Single Dose Creatine Improves Cognitive Performance and Induces Changes in Cerebral High Energy Phosphates During Sleep Deprivation. *Scientific Reports*. Vol. 14, No. 4937, pp. 1-15.

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Abstract Summary: This study investigated the effects of a single high dose of creatine monohydrate on cerebral high energy phosphates and cognitive performance during partial sleep deprivation, suggesting that acute creatine administration can partially reverse metabolic alterations and fatigue-related cognitive deterioration.

Key Methodology: Randomized, controlled, double-blinded cross-over trial with 15 healthy subjects; oral administration of a single high dose of creatine monohydrate (0.35 g/kg) or placebo; sub-total 21 hours of sleep deprivation; measurements using ${}^{31}extP-MRS$, ${}^{1}extH-MRS$, and a battery of cognitive tests (PVT, WMT, SPAN, multiple-choice tasks) at four time points.

Research Question: Can a high extracellular availability of creatine, achieved through a single high dose, temporarily increase central creatine uptake and compensate for metabolic changes and cognitive impairment during sleep deprivation?

Summary

Is It Credible?

The study by Gordji-Nejad et al. presents a provocative challenge to the established consensus on creatine supplementation. While prevailing literature suggests that creatine requires weeks of loading to significantly increase brain concentrations and influence cognition, this article claims that a "single high dose of creatine" (0.35 g/kg) can induce rapid "changes in cerebral high energy phosphates" and improve cognitive performance during sleep deprivation (p. 1). The authors report that this acute intervention prevented a drop in cerebral pH, altered ATP dynamics, and mitigated fatigue-induced deficits in memory and processing speed (p. 1). If true, these findings would fundamentally alter our understanding of blood-brain barrier kinetics and offer a viable acute countermeasure for sleep loss. However, a rigorous assessment of the methodology reveals several limitations that complicate these conclusions.

The credibility of the cognitive findings is strained by the choice of placebo. The study utilized corn starch as the control substance (p. 2). While the authors likely intended this as a standard inert filler, corn starch is a carbohydrate that metabolizes into glucose, whereas creatine does not. In the context of an overnight study involving sleep deprivation—a state known to alter glucose metabolism—providing one group with a complex carbohydrate and the other with a non-caloric supplement introduces a significant metabolic variable. The study essentially compares a phosphagen energy buffer against a glycolytic substrate. Any difference in cognitive performance could plausibly be attributed to the differential glycemic impact of the placebo rather than the specific neurochemical properties of creatine. Furthermore, the sheer volume of the dose (approximately 25–30g for an average adult) raises questions about the integrity of the double-blind design. Although the authors state

that "No gastric discomfort or other physical complaint was signalized" (p. 6), high-dose creatine is frequently associated with water retention and bloating. Without a formal assessment of blinding success (e.g., asking participants to guess their condition), it remains possible that subtle somatic cues influenced participant expectancy, which is particularly potent in subjective measures of fatigue and effort-dependent cognitive tasks.

The metabolic evidence for acute brain uptake is similarly fragile. The claim that creatine is "readily bioavailable to the brain" rests largely on an observed increase in the total creatine to total N-acetylaspartate ratio (tCr/tNAA) (p. 11). However, this effect was statistically significant in only one specific brain region (the left medial parietal region), and data from the frontal lobe was largely excluded due to technical limitations with shimming (p. 6). Crucially, this ratiometric analysis assumes that tNAA remains a stable reference during sleep deprivation. While the authors present supplementary data suggesting stability (Table S9), if the stress of sleep loss alters tNAA levels even marginally, the ratio could change without any actual increase in cerebral creatine. Additionally, the study reports a decrease in ATP levels following creatine administration (p. 8). The authors reasonably attribute this to the creatine kinase equilibrium shifting toward phosphocreatine production (p. 12); however, in the context of sleep deprivation, where energy maintenance is critical, the physiological implications of a lower standing ATP concentration warrant more critical discussion than is provided.

Finally, the statistical robustness of the findings is open to question. The sample size is small ($N = 15$), and the authors acknowledge the risk of Type II errors (p. 5). More concerning is the approach to multiple comparisons. The analysis involved numerous brain voxels, metabolites, and cognitive tests. The Bonferroni correction was applied based on the number of conditions (time points x sessions) rather than the total number of spatial comparisons (voxels) (p. 5). While Bonferroni is typically conservative, applying it to the experimental conditions rather than the high-

dimensional spatial data may not adequately control the false positive rate across the entire brain volume. Consequently, while the study generates an interesting hypothesis regarding acute creatine use, the evidence is currently insufficient to definitively overturn the consensus that brain uptake is a slow, chronic process.

The Bottom Line

The claim that a single dose of creatine provides acute cognitive protection against sleep deprivation is not yet fully credible. The results are likely confounded by the use of a glucose-releasing placebo (corn starch), which creates a comparison between two different energy substrates rather than a true inert control. Furthermore, the metabolic evidence for rapid brain uptake relies on indirect ratios in isolated brain regions and is statistically fragile, failing to definitively prove that the supplement crossed the blood-brain barrier in meaningful quantities across the whole brain.

Potential Issues

Inadequate correction for multiple comparisons: The study's statistical approach may be insufficient for the volume of spatial tests conducted, raising the risk of false positive findings. The authors state they applied a Bonferroni correction for eight conditions ($\alpha = 0.05/8 = 0.0063$), corresponding to the four time points in two sessions (p. 5). However, applying this single threshold to the numerous brain regions and voxels tested may not adequately control the overall error rate. The analysis involved at least 36 distinct voxels from ^{31}P-MRS (p. 4). A voxel-wise analysis of this nature would typically require a correction that accounts for the spatial dimension of the data, such as a family-wise error correction or cluster-based thresholding, to control the false positive rate across the entire brain volume. By correcting primarily for the number of experimental conditions, the study may have used a significance threshold that was too lenient for the exploratory nature of the brain mapping.

Potential confounds in the experimental design: Several aspects of the study design introduce plausible alternative explanations for the observed results. First, the study used corn starch as a placebo (p. 2). Corn starch is a carbohydrate that is metabolized into glucose, while creatine is not. In an overnight fasting state, this difference leads to distinct effects on blood glucose and insulin. While the study aims to compare these energy sources, the differential glycemic impact acts as a significant variable that complicates the isolation of creatine's specific neuroprotective effects. Second, the study did not report controlling for hydration status. Creatine supplementation can increase water retention; if the creatine group consumed more fluids than the placebo group, their cognitive performance could be partly due to better hydration. Third, the order of testing was different at baseline compared to follow-up. At baseline, cognitive tests were performed before the MRS scan, whereas at follow-up, they were performed after the ~75-minute scan (p. 2). The authors state this was to prevent fatigue from affecting metabolic measures (p. 2), but this procedural difference

means that follow-up cognitive performance was measured after a period of lying supine in a scanner, a state which could affect alertness differently than at baseline.

The primary evidence for acute brain creatine uptake is indirect and regionally isolated: The study's central claim that a single high dose of creatine is rapidly bioavailable to the brain rests on limited evidence. The main direct finding is an increase in the total creatine to total N-acetylaspartate ratio (tCr/tNAA) observed via ^{1}H-MRS, an effect that was statistically significant only in the left medial parietal region (p. 6). Data from the frontal lobe was largely unusable due to technical challenges, preventing corroboration in another key area (p. 6). Crucially, this conclusion assumes that tNAA is a stable reference metabolite throughout the 21-hour sleep deprivation protocol. While the authors provide supplementary data on metabolite stability (Table S9), relying on a ratio where the denominator may fluctuate under stress introduces ambiguity. If sleep deprivation itself alters tNAA levels, the change in the tCr/tNAA ratio could be driven by the denominator rather than an increase in creatine.

Ambiguous quantification of MRS data: The study's analysis of high-energy phosphates relies on ratiometric methods that may be difficult to interpret. For some key results, the denominator is the total phosphorus signal (^{31}P), defined as the sum of signals from PCr, ATP-β, Pi, and other phosphates (p. 4). This method is only valid if the denominator remains stable across conditions. However, the study's central hypothesis and findings are that the intervention alters the levels of PCr, ATP, and Pi. If these major components of the total phosphorus signal are changing, their sum is also likely to change, making it an unstable reference. This introduces a fundamental ambiguity, as a change in a ratio like ATP-$\beta/^{31}$P could be caused by a change in ATP, a change in the total pool, or both.

Insufficient justification for sample size and missing data: The study's small sample size ($N = 15$) is justified by a power calculation assuming an exceptionally large effect size of 1.33 (p. 5), which may not be realistic for many cognitive and metabolic

outcomes. Consequently, the study was likely underpowered for detecting more modest effects. This issue is compounded by the exclusion of data from the frontal lobe for most subjects due to technical difficulties with ^{1}H-MRS shimming, with usable data available from "only 6 subjects" for that specific measurement (p. 6). While this exclusion was for technical reasons rather than participant dropout, it significantly reduces the statistical power and representativeness of the findings for that brain region.

Pattern of imprecision in statistical and data reporting: The article exhibits a pattern of inconsistencies and omissions that complicates verification of the results. First, the statistical notation is unconventional. For example, *t*-statistics are reported with subscripts that appear to refer to time-point comparisons (e.g., t_{12}, t_{43}) rather than degrees of freedom (p. 6), which is non-standard and can be confusing. Second, a data transformation was applied to some of the primary metabolic data but was only disclosed in the supplementary materials. The supplement states that data from the upper grid for PCr/^{31}P and ATP-β/^{31}P "were scaled with factors of 1.1... and 1.3... for better visual compensation" (Supplementary p. 22). While this likely refers to the visual presentation in figures rather than the statistical analysis itself, the placement of this data processing detail outside the main text is a methodological omission that hinders reproducibility.

Questionable blinding procedure: The study used a high dose of creatine (0.35 g/kg), which can be associated with gastrointestinal side effects, while the placebo was inert corn starch (p. 2). Although the authors report that "No gastric discomfort or other physical complaint was signalized" (p. 6), they do not report having formally assessed the success of the blinding procedure, for instance by asking participants to guess their assigned condition. Without this formal check, it is difficult to rule out the possibility that subtle somatic cues influenced participant expectancy.

Future Research

Control for glycemic and sensory confounds: Future work must utilize a placebo that is matched not only in appearance but also in caloric content and glycemic index to rule out glucose-mediated cognitive preservation. Additionally, given the high dose required, the study design should include a formal assessment of blinding efficacy to ensure that subtle somatic cues did not influence participant expectations.

Direct measurement of uptake: To confirm the controversial claim of acute brain bioavailability, researchers should employ Carbon-13 (^{13}C) magnetic resonance spectroscopy. This method allows for the direct tracking of isotopically labeled exogenous creatine as it enters the brain, distinguishing it from endogenous stores and eliminating the ambiguity inherent in ratio-based measures like tCr/tNAA.

Robust statistical mapping: Subsequent studies should employ a larger sample size and pre-registered statistical analysis plans that utilize cluster-based thresholding or similar rigorous corrections for multiple comparisons across the entire brain volume. This is necessary to determine whether metabolic changes are truly global and physiological, or merely statistical artifacts arising from high-dimensional data analysis in a small cohort.

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