Creatine, the brain, and cognition

A critical research report on neuroenergetics, cognitive performance, sleep loss, aging, mental health, neurological disease, safety, and the limits of current evidence

Bottom line: creatine monohydrate can raise brain creatine, but oral supplementation has not been shown to improve cognition reliably in the general healthy population. Small benefits are plausible - especially for memory or when cerebral energy demand is stressed - yet the best regulatory assessment found that a cause-and-effect cognition claim is not established.

Executive judgment

Evidence area	What the studies show	Assessment
Biological plausibility	The creatine-phosphocreatine system buffers ATP, moves energy between mitochondria and sites of use, and is essential to normal brain function.	**Strong**
Brain exposure	Magnetic resonance spectroscopy studies show that oral creatine can increase brain total creatine, usually modestly and less predictably than muscle creatine.	**Moderate**
Healthy cognition	Trials are small and heterogeneous. The largest preregistered trial found, at most, a small effect; EFSA judged the total evidence insufficient for a causal claim.	**Uncertain / small at most**
Energy stress	Signals are more consistent during sleep deprivation and possibly hypoxia or demanding tasks, but the evidence base remains sparse.	**Promising, preliminary**
Clinical treatment	No established role for treating dementia, Parkinson disease, Huntington disease, ALS, TBI, or depression. Some pilot signals deserve trials; large neurodegeneration trials have often been negative.	**Not established**
Safety	Creatine monohydrate is generally well tolerated in healthy adults. Weight gain and gastrointestinal effects occur; serum creatinine can rise without true kidney injury.	**Generally reassuring**

The practical reading

Creatine is not a proven nootropic in the way that marketing language often implies. For a healthy adult who already chooses it for muscle or training benefits, a small cognitive benefit is possible but should be treated as a bonus, not an expectation. It should not replace sleep, medical evaluation, or evidence-based treatment.

Scope: human evidence receives greatest weight. Animal and cellular findings are included only to explain mechanisms or future directions. This is educational synthesis, not personal medical advice.

How this report was built

The evidence search prioritized systematic reviews, meta-analyses, randomized controlled trials, major negative phase III trials, regulatory assessments, and authoritative safety material. Sources were searched through 2 September 2026. Particular weight was given to EFSA's 2024 scientific opinion because it independently examined the proposed cognition claim and exposed a unit-of-analysis flaw in a favorable 2024 meta-analysis.

Questions covered

- What creatine is, where it comes from, and why the brain needs it.
- Whether supplements measurably raise brain creatine.
- Effects on memory, attention, processing speed, executive function, intelligence, mood, fatigue, and sleep-loss performance.
- Whether age, diet, sex, baseline status, dose, or stress changes response.
- Evidence in depression, Alzheimer disease, Parkinson disease, Huntington disease, ALS, TBI, and cerebral creatine deficiency syndromes.
- Dosing patterns studied, safety, laboratory interpretation, and product-quality issues.

Evidence hierarchy and language

Label	Meaning	Use
Established	Consistent evidence or accepted physiological fact.	**High confidence**
Suggestive	A signal exists, but replication, precision, or generalizability is limited.	**Moderate / low**
Preliminary	Pilot, uncontrolled, subgroup, or stress-specific evidence.	**Low / very low**
Not established	Null, contradictory, methodologically inadequate, or insufficient human evidence.	**Do not infer benefit**

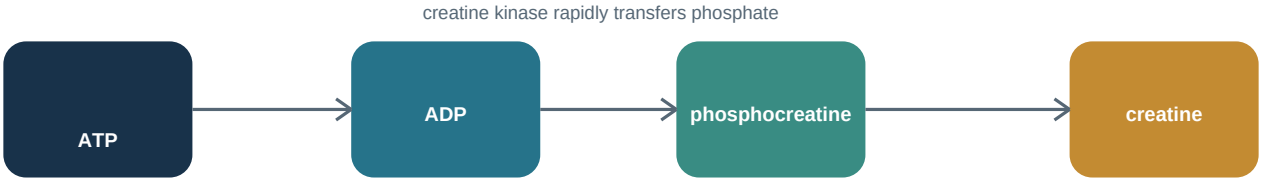
Important limitations

- Cognition is not one outcome. A supplement can affect one timed task and do nothing for memory, executive function, learning, or everyday performance.
- Many trials test numerous correlated outcomes in small samples. Selective significance and multiplicity can create apparently persuasive results.
- Brain creatine is usually inferred by proton magnetic resonance spectroscopy. Total creatine concentration is a biomarker, not proof of better function.
- Trials use different diets, populations, doses, durations, washouts, and cognitive batteries. Pooling can obscure rather than solve these differences.
- A statistically significant change may be too small to notice or matter clinically.

Proof boundary: mechanism is not efficacy; brain uptake is not cognitive improvement; a laboratory task is not academic or occupational performance; an association is not a treatment recommendation.

1. Creatine biology in the brain

Creatine is a nitrogen-containing organic compound synthesized mainly from arginine, glycine, and methionine. The kidneys and pancreas participate in early synthesis and the liver contributes methylation; tissues also obtain creatine from meat and fish. Most body creatine is in skeletal muscle, but the brain contains its own tightly regulated pool and can synthesize some locally.



The system buffers energy demand; supplementation does not guarantee better cognition.

The phosphocreatine shuttle

When ATP is used, it becomes ADP. Creatine kinase can transfer a phosphate from phosphocreatine to ADP, rapidly regenerating ATP. Mitochondrial and cytosolic creatine kinase isoenzymes help buffer rapid changes in energy demand and move high-energy phosphate equivalents across the cell. In neurons and glia, this is relevant to membrane ion pumps, neurotransmission, synaptic plasticity, axonal transport, and maintenance of electrochemical gradients.

What creatine might influence

Evidence area	What the studies show	Assessment
Energy buffering	Maintains ATP/ADP balance during fluctuating demand; the most direct and defensible mechanism.	**Established physiology**
Mitochondria	May stabilize energy handling and reduce energetic failure in experimental systems.	**Plausible; clinical translation weak**
Oxidative stress	Direct and indirect antioxidant effects are reported in preclinical work.	**Mechanistic, not clinical proof**
Excitotoxicity	Energy support could help ion pumps and glutamate handling under stress.	**Preclinical hypothesis**
Osmotic effects	Creatine is an osmolyte and draws water into cells; this may affect signaling and volume regulation.	**Biologically plausible**
Neurotransmission	Associations with glutamate, GABA, dopamine, and serotonin systems are proposed.	**Indirect / inconsistent**

Why deficiency syndromes matter

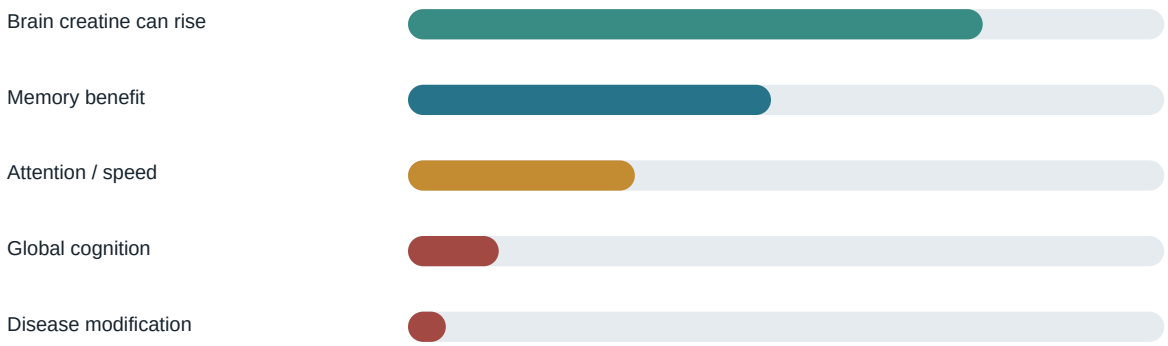
Rare inherited defects in creatine synthesis (GAMT or AGAT deficiency) or transport (SLC6A8 deficiency) cause very low cerebral creatine and can produce intellectual disability, speech delay, seizures, and behavioral abnormalities. This is compelling evidence that creatine metabolism is necessary for normal brain development. It does **not** show that raising creatine above an adequate baseline enhances a healthy brain. Synthesis defects can respond to specialist treatment; transporter deficiency is much harder because oral creatine cannot readily cross the missing transporter pathway.

2. From powder to brain: uptake is the bottleneck

Creatine monohydrate is well absorbed from the gut and reliably raises blood and muscle creatine. The brain is different. The blood-brain barrier and creatine transporter limit entry, cerebral concentrations are tightly regulated, and the brain also synthesizes creatine. Consequently, muscle-loading protocols cannot be assumed to load the brain to the same degree or on the same timetable.

What human spectroscopy shows

- Across human magnetic resonance spectroscopy studies, supplementation can raise brain total creatine, but the average increase is often modest and some participants or regions show little change.
- Longer or higher-dose protocols may be needed than for muscle, but the optimal regimen is not known.
- Baseline concentration, region, age, diet, disease state, transporter expression, and measurement technique may influence the observed response.
- A 2025 single-arm Alzheimer pilot using 20 g/day for 8 weeks reported an 11% rise in brain total creatine. Without placebo control, the simultaneous cognitive improvement cannot establish efficacy.
- A 2024 sleep-deprivation crossover trial reported acute changes in cerebral high-energy phosphate measures after a single high dose; this is provocative but not a general dosing recommendation.



Conceptual confidence map, not a quantitative probability scale.

Why biomarker response and cognition can diverge

Evidence area	What the studies show	Assessment
Adequate baseline	If cerebral energy buffering is already sufficient, more substrate may not improve performance.	**Ceiling effect**
Regional mismatch	A global or voxel-average rise may not occur in the network limiting the tested task.	**Measurement issue**
Wrong task	Benefits might emerge only at high demand, while easy tasks leave ample energetic reserve.	**Design issue**
Time course	Blood, muscle, and brain pools may saturate on different schedules.	**Regimen issue**
Non-response	Transport and synthesis regulation may blunt brain uptake in some people.	**Biological heterogeneity**

A future decisive trial should measure baseline and post-treatment brain creatine, preregister one primary cognitive endpoint, use enough participants, and test both rested and energy-stressed conditions.

3. Cognition in healthy adults

The overall literature contains genuine positive findings, genuine null findings, and methods that make the positive side look more certain than it is. The safest synthesis is that any average benefit in rested, healthy adults is probably small, domain-specific, and not reliably demonstrated.

The strongest recent conflict

Evidence area	What the studies show	Assessment
2024 meta-analysis	Sixteen RCTs, 492 participants. Reported small improvements in memory (SMD 0.31), attention time, and processing-speed time; no significant effect on global cognition or executive function. Memory was graded moderate certainty; other domains low.	**Favorable, but flawed**
EFSA 2024	Reviewed 23 intervention studies. Found that the meta-analysis pooled multiple related tests from the same participants as if independent, double-counting participants and inflating sample size. Concluded no cause-and-effect cognition claim was established.	**Most cautious synthesis**
McMorris et al. 2024	Systematic review concluded brain creatine can rise, but cognitive results in healthy people were equivocal, with little effect in non-stressed participants.	**Consistent with uncertainty**
Sandkuehler et al. 2023	Largest preregistered cognition RCT: 123 adults, 5 g/day for 6 weeks in crossover design. Bayesian evidence suggested a small effect; backward digit span bordered significance, Raven reasoning and eight exploratory tests were null.	**Small effect at most**

Domain-by-domain

Evidence area	What the studies show	Assessment
Memory	The most recurrent positive signal, especially short-term or working memory. A 2022 meta-analysis favored memory overall, with stronger signals in older adults; small trials and heterogeneity limit confidence.	**Possible small benefit**
Reasoning / intelligence	The classic 2003 vegetarian crossover trial found better Raven matrices and backward digit span; the larger 2023 replication found no significant Raven effect.	**Not reliably replicated**
Attention	Some timed measures improve, others do not. Accuracy, sustained attention, and inhibition are inconsistent.	**Low certainty**
Processing speed	Some meta-analytic timed outcomes favored creatine, but heterogeneous tasks and non-independent pooling weaken the estimate.	**Low certainty**
Executive function	Recent synthesis and EFSA review do not support a reliable improvement.	**No established effect**
Everyday performance	No convincing evidence that creatine raises grades, work output, complex learning, or long-term functional achievement.	**Unknown**

4. Who might respond differently?

The energy-reserve hypothesis predicts larger effects when baseline creatine is lower or demand is higher. That prediction is reasonable, but subgroup evidence is too sparse to identify a dependable 'responder' profile.

Vegetarians and vegans

Because meat and fish supply dietary creatine, vegetarians often have lower muscle creatine. The 2003 Rae trial in 45 vegetarians found strong working-memory and reasoning effects after 5 g/day for 6 weeks. Later trials did not consistently reproduce a diet interaction: the 2023 study, with about half vegetarians, found no greater benefit in vegetarians. Lower dietary intake is therefore a plausible moderator, not a proven predictor of cognitive response.

Age

Older adults may have lower dietary intake, altered energetics, or less physiological reserve. A small 2007 study reported broad cognitive improvement after 20 g/day for one week, whereas a 24-week trial in older women found no cognitive effect. A 2025 systematic review identified only six studies, four observational, and judged the evidence limited despite mostly positive associations. Associations between dietary creatine and cognition cannot separate creatine from diet quality, protein intake, socioeconomic factors, or health.

Sex

Some subgroup analyses suggest larger effects in females, and sex-related differences in creatine synthesis, diet, hormones, and brain energetics are biologically possible. Current trials were not designed or powered to establish sex-specific efficacy, so this remains hypothesis-generating.

Baseline cognitive or metabolic stress

Evidence area	What the studies show	Assessment
Sleep deprivation	Several small studies report less fatigue or better performance on selected tasks. A 2024 crossover trial combined cognitive testing with phosphorus/proton MRS after an acute high dose.	**Most promising stress model**
Hypoxia	Small experimental studies suggest possible benefit when oxygen availability constrains ATP production.	**Preliminary**
Hard tasks	Benefits may be easier to detect on complex, high-load tasks than simple reaction time.	**Plausible, inconsistent**
Low dietary creatine	Vegetarian status may raise response probability, but a large recent trial did not confirm moderation.	**Uncertain**
Disease / aging	Energetic impairment may create a larger therapeutic window, but disease trials often fail despite strong mechanisms.	**Cannot assume benefit**

The most defensible hypothesis is conditional: creatine may help some cognitive tasks when energy demand exceeds reserve. It is not yet a validated rule for selecting people or doses.

5. Sleep deprivation, fatigue, and mood

Sleep loss is the clearest setting in which the energy-buffer model has produced a coherent human signal. Sleep deprivation alters brain energy metabolism and degrades attention, executive control, psychomotor speed, and mood. Creatine may reduce some of that decline, but it does not restore the many hormonal, synaptic, immune, and memory-consolidation functions of sleep.

The acute high-dose study

In a randomized, double-blind, placebo-controlled crossover experiment during partial sleep deprivation, a single dose of 0.35 g/kg altered cerebral creatine and high-energy phosphate measures, reduced subjective fatigue, and improved selected cognitive outcomes relative to placebo. The design is scientifically valuable because it connects target engagement to performance. It is also a small, unusual, high-dose laboratory protocol - not evidence for routine self-treatment or a substitute for sleep.

Evidence area	What the studies show	Assessment
What is supported	Creatine may attenuate deterioration on selected tasks during acute sleep loss.	**Early positive signal**
What is not supported	It has not been shown to restore normal cognition, consolidate memory, prevent accidents, or eliminate the health effects of insufficient sleep.	**No**
Research gap	Few trials, different deprivation protocols, doses, outcomes, and small samples.	**High uncertainty**

Mood and depression

Creatine has been studied as an adjunct in depression, partly because altered cerebral bioenergetics is observed in some patients. A 2025 systematic review and meta-analysis of 11 trials (1,093 participants) estimated a small-to-moderate standardized effect, equivalent to about 2.2 points on the 17-item Hamilton Depression Rating Scale - below its prespecified 3-point minimal important difference. Evidence quality was very low, heterogeneity substantial, and bias analyses favored creatine. The true average effect may be trivial or null.

- Remission favored creatine in three small trials, but treatment response did not in two trials.
- Some studies combined creatine with antidepressants; this tests adjunctive therapy, not creatine alone.
- Depression is clinically heterogeneous, and a supplement should not delay professional assessment or evidence-based care.
- There is no established evidence that creatine treats anxiety, bipolar disorder, psychosis, or ADHD cognition.

Clinical boundary: preliminary depression data do not justify starting, stopping, or changing psychiatric treatment without the prescribing clinician.

6. Neurological and neurodegenerative conditions

Creatine has an unusually instructive translational history: animal models and biomarkers often looked promising, yet large clinical trials frequently failed. This is a warning against equating neuroprotection in cells or mice with meaningful human disease modification.

Evidence area	What the studies show	Assessment
Alzheimer disease	A 2025 single-arm pilot (20 participants, 20 g/day, 8 weeks) found high adherence, an 11% brain-creatine rise, and improved test scores. Without placebo control, practice effects and regression to the mean cannot be excluded.	**Feasible; efficacy unknown**
Parkinson disease	A large long-term randomized trial found no improvement in clinical outcomes and was stopped early for futility. Creatine is not supported as disease-modifying therapy.	**Negative phase III**
Huntington disease	Early biomarker findings encouraged large trials. CREST-E randomized 553 people to up to 40 g/day and was halted for futility; functional decline did not improve.	**Negative phase III**
ALS	Three randomized trials (386 participants in a Cochrane synthesis) found no survival or progression benefit at 5-10 g/day.	**No clinical benefit**
TBI / concussion	A small open-label randomized pediatric pilot reported improvements in several symptoms after 0.4 g/kg/day for 6 months. Design, size, age group, and dated evidence preclude routine recommendation.	**Very preliminary**
Cerebral creatine deficiency	Specialist treatment can be important in synthesis defects; transporter deficiency responds poorly to oral creatine. This rare disease evidence is not transferable to healthy enhancement.	**Distinct medical indication**

Alzheimer pilot: how to read it correctly

- The 11% MRS rise demonstrates target engagement under that regimen.
- Improvement from baseline in an uncontrolled trial does not separate treatment from learning the tests, attention from study staff, natural fluctuation, or selection.
- The study supports a randomized placebo-controlled efficacy trial. It does not support use as Alzheimer treatment today.

Why neurodegeneration trials may fail

- Energy dysfunction may be downstream rather than causal.
- Treatment may begin after irreversible neuronal loss.
- Brain uptake may be insufficient or regionally mismatched.
- The pathway may matter only in subgroups that trials do not enrich.
- Animal disease models may not capture human pathology or timescale.
- Biomarker changes can occur without functional benefit.

7. Regimens studied and practical safety

Creatine monohydrate is the reference form: it dominates the evidence, is chemically well characterized, and is usually less expensive than marketed alternatives. Claims that buffered, nitrate, hydrochloride, or other forms are superior for the brain are not supported by comparable clinical evidence.

Study regimens are not one standard

Evidence area	What the studies show	Assessment
Maintenance-style	About 3-5 g/day for weeks or months. Common in exercise research; brain response may be slow or small.	**Best studied generally**
Loading-style	About 20 g/day divided for 5-7 days, sometimes followed by 3-5 g/day.	**Used in several cognition trials**
High / clinical	10-40 g/day or weight-based dosing in sleep-loss or disease research.	**Research protocols only**
Acute	Single high doses during sleep deprivation.	**Experimental; not routine guidance**

The report does not prescribe a cognitive dose because no regimen has established a general cognitive benefit, and high-dose research protocols can increase gastrointestinal effects and should not be copied casually.

Common and interpretive issues

Evidence area	What the studies show	Assessment
Weight gain	Usually reflects increased body water, especially during loading; muscle accretion may contribute over time with training.	**Common**
Gastrointestinal upset	Nausea, diarrhea, bloating, or cramping may occur, especially with large single doses.	**Dose-related**
Serum creatinine	Can rise because creatine converts to creatinine. Creatinine-based eGFR may therefore look worse without kidney injury.	**Important lab artifact**
Kidney injury	Recent meta-analyses found no meaningful decline in measured or non-creatinine kidney function in studied populations, but very long-term and high-risk evidence is thinner.	**Reassuring, not universal**
Dehydration / cramps	Controlled evidence does not support a general increase; individuals can still have symptoms for unrelated reasons.	**Common myth**
Hair loss	Concern derives mainly from one small study of DHT, not trials measuring hair loss. A causal effect is unproven.	**Not established**

Who should seek clinical advice first

- Known kidney disease, reduced kidney function, unexplained abnormal kidney tests, or a history of kidney injury.
- Pregnancy or breastfeeding, children and adolescents, or frail older adults, because evidence and context differ.
- Use of medicines that affect renal function or fluid balance, or complex chronic disease.

- Bipolar disorder or significant psychiatric instability, because limited case reports and adjunctive trials do not establish safety for every presentation.
- Upcoming blood tests: tell the clinician and laboratory about creatine so serum creatinine is interpreted appropriately.

Product quality matters. In Australia, supplements are regulated as therapeutic goods but evidence and manufacturing oversight vary by product. Prefer a simple creatine monohydrate product from a reputable supplier with independent contaminant testing; avoid proprietary 'brain blends' that obscure doses.

8. Claims audit: what is true, exaggerated, or unknown

Evidence area	What the studies show	Assessment
'Creatine fuels the brain'	Broadly true: the creatine kinase system buffers cerebral ATP.	**Mechanism established**
'It raises IQ'	One small vegetarian trial improved a reasoning test; the larger replication did not show a significant Raven effect.	**Overstated**
'It improves memory'	The most plausible cognitive claim, with small pooled effects, but the meta-analytic literature has important bias and independence problems.	**Possible, not assured**
'Vegans benefit most'	Lower dietary intake makes sense biologically, but recent trial evidence did not confirm a larger cognitive response.	**Plausible, unproven**
'It replaces sleep'	It may blunt selected impairments during acute sleep loss; it cannot reproduce sleep's biological functions.	**False**
'It treats dementia'	An uncontrolled Alzheimer pilot is encouraging, while established neurodegeneration programs have often failed.	**Not established**
'It damages kidneys'	Usual studied doses have not shown kidney damage in healthy adults, though serum creatinine may rise and high-risk groups need individualized advice.	**Generally false / nuanced**
'More is better for the brain'	Brain uptake may require different regimens, but higher doses increase burden and have not established superior real-world benefit.	**Unsupported**

A sensible decision framework

Evidence area	What the studies show	Assessment
Goal	If the goal is proven cognitive enhancement in a rested healthy adult, evidence is insufficient. If already using creatine for training, cognition can be treated as an uncertain secondary possibility.	**Set expectations**
Form	Creatine monohydrate has the evidence base; exotic forms add cost without proven brain advantage.	**Simplify**
Baseline	Record sleep, diet, medication, kidney history, body weight, and a meaningful outcome before attributing changes.	**Reduce self-deception**
Trial	Do not change multiple supplements simultaneously; avoid interpreting day-to-day task practice as an effect.	**Better inference**
Stop / review	Persistent GI symptoms, edema, concerning mood change, or abnormal clinical findings deserve review.	**Safety**

What would change the conclusion?

- Several large, preregistered, independently funded RCTs with one primary outcome and adequate multiplicity control.
- Demonstrated brain target engagement tied prospectively to cognitive benefit.
- Replication in clearly defined populations: older adults, vegetarians/vegans, sleep-deprived workers, or mild cognitive impairment.
- Evidence that changes persist, transfer to everyday function, and exceed practice effects.
- Longer safety follow-up in clinically vulnerable populations.

9. Research agenda

The field is no longer limited by plausible stories. It is limited by trial architecture.

Evidence area	What the studies show	Assessment
Population	Stratify by age, habitual creatine intake, sex, baseline brain creatine, sleep, and metabolic disease before randomization.	**Who responds?**
Target engagement	Use harmonized MRS methods and report region-specific absolute changes, not only ratios.	**Did it reach brain?**
Dose	Compare 3-5 g/day, loading, and longer high-dose regimens with safety and tolerability endpoints.	**How much / how long?**
Cognition	Select one primary domain, use validated alternate forms, and control family-wise error for secondary tests.	**Avoid false positives**
Stress	Factorial designs can test rested versus sleep-deprived or hypoxic states in the same protocol.	**Conditional benefit**
Function	Add learning retention, driving or occupational simulations, patient function, and quality of life.	**Does it matter?**

Evidence area	What the studies show	Assessment
Transparency	Publish protocols, analysis code, null outcomes, adverse events, and industry roles.	**Trustworthy evidence**

A model definitive healthy-adult trial

- At least several hundred participants, stratified by diet and age.
- Parallel groups long enough for brain loading, with a prespecified loading sub-study.
- Baseline and end-point MRS in a sufficiently powered subset.
- One primary cognitive composite constructed before unblinding; no double-counting of correlated tests.
- Rested and controlled sleep-restriction sessions.
- Objective adherence, adverse events, body mass, serum creatinine plus cystatin C or measured filtration in a safety subset.
- Follow-up after washout to test persistence.

Final synthesis

Creatine is essential brain chemistry and a credible experimental tool for cerebral bioenergetics. It may provide a small cognitive advantage in some people or under energetic stress. But as of September 2026, it is not a generally proven cognitive enhancer or an established treatment for neuropsychiatric or neurodegenerative disease.

The evidence is strong enough to justify better trials and weak enough to resist confident marketing claims. That tension - impressive physiology, modest brain uptake, heterogeneous task effects, and repeated clinical translation failures - is the central fact of the field.

Educational use only. A clinician or pharmacist should individualize advice where kidney disease, pregnancy, youth, psychiatric illness, interacting medicines, or abnormal laboratory results are relevant.

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Search cut-off: 2 September 2026. This report is a critical narrative synthesis, not a formal PRISMA systematic review. It does not claim exhaustive capture of every preclinical paper or conference abstract.