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BEYOND AGE-BASED BRAIN HEALTH

A Neuroadaptive Framework for Memory and Focus Across Generations

From cognitive enhancement to state-dependent precision nutrition

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CORE PROPOSITION

The next generation of cognitive nutrition should be formulated against the biological process that becomes limiting under a defined cognitive state - not against chronological age or an undifferentiated promise of “brain health.”

ARTICLE TYPE

Perspective / translational research framework

Novel concepts introduced: Cognitive Load–Reserve Matching (CLRM), state-dependent cognitive nutrition, chronocognitive nutrition, closed-loop neuroadaptive nutrition, and the cognitive digital twin. These are research frameworks, not established clinical doctrines.

Abstract

The market for memory and focus interventions is undergoing a fundamental demographic and scientific transition. Cognitive-health products were historically positioned around ageing, memory loss and preservation of function in older adults. Demand now encompasses adolescents exposed to high digital and academic loads, university students, cognitively demanding professionals, shift workers, sleep-restricted adults, midlife women experiencing reproductive transitions, and older individuals seeking to preserve cognitive resilience. Yet formulation science has not fully adapted: most products remain organised around broad age categories or ingredient accumulation rather than around the physiological constraint that is actually limiting cognitive performance.

This Perspective proposes **Cognitive Load–Reserve Matching (CLRM),** a translational framework in which nutritional interventions are selected according to the interaction between cognitive demand, physiological reserve, state disruptors, cognitive domain and time scale. Under this model, an intervention need not improve cognition in every rested, well-nourished individual to be biologically relevant. It may instead preserve performance selectively when brain-energy availability, sleep-dependent recovery, attentional control, neuronal membrane function, visual-neural efficiency, neurovascular responsiveness or metabolic flexibility becomes limiting.

Recent human evidence supports this state-dependent interpretation. Creatine has produced clearer cognitive effects under sleep deprivation than in rested healthy adults; lutein and zeaxanthin have generated cognitive signals in younger adults and, recently, teenagers with high screen exposure and low fruit and vegetable intake; omega interventions in adolescents illustrate why target-engagement biomarkers and analysis discipline matter; citicoline has shown domain-specific signals in adolescent males and older adults; ketogenic substrates appear most relevant where cerebral energetic vulnerability is present; and a recent Bacopa trial failed on its primary cognitive endpoints while improving stress reactivity and post-task fatigue. These patterns argue against a universal nootropic and in favour of phenotype-, state- and task-adaptive cognitive support.

We therefore propose *chronocognitive delivery*, biomarker-linked validation, digital cognitive phenotyping, challenge-based trials and closed-loop intervention models as the next research frontiers. The resulting field would be less about ingredient stacking and more about matching mechanism, timing and evidence to the cognitive state that needs support.

Keywords: *cognitive nutrition; memory; attention; executive function; cognitive resilience; precision nutrition; nootropics; digital biomarkers; creatine; citicoline; lutein; zeaxanthin; omega-3; sleep; ketones; cognitive ageing.*

EVIDENCE-READING RULE

Throughout this article, human clinical findings are separated from mechanistic plausibility and from hypotheses proposed for future research. A plausible mechanism is not presented as proof of efficacy, and evidence from clinical populations is not automatically extrapolated to healthy consumers.

The multi-generational problem is biologically heterogeneous

Phenotype	Likely limiting context	Priority cognitive domains	Useful measurement layer
High-screen adolescent	Visual/cognitive overload; insufficient sleep; developmental executive control	Attention, processing speed, inhibitory control	MPOD; Omega-3 Index; actigraphy
Student / young professional	Prolonged cognitive load; variable sleep; stimulant dependence	Vigilance, working memory, task switching	PVT variability; sleep/HRV; exposure markers
Shift worker / sleep restricted	Acute energetic and circadian stress	Reaction time, processing speed, reasoning	Actigraphy; circadian timing; mechanistic MRS in substudies
Midlife transition	Sleep, stress, reproductive-stage and metabolic interactions	Verbal learning, working memory, attention	Reproductive staging; sleep; symptom phenotype; metabolic markers
Healthy older adult	Declining reserve without clinical impairment	Processing speed, episodic memory, resilience	Nutrient status; digital variability; vascular/metabolic markers

Phenotype	Likely limiting context	Priority cognitive domains	Useful measurement layer
MCI / clinical vulnerability*	Reduced metabolic flexibility and/or early pathological change	Memory, executive function, global cognition	Clinical diagnosis; ketone response; imaging / biochemical markers

*Table 1. Illustrative phenotypes. *Clinical populations require separate diagnostic, ethical and regulatory treatment; evidence cannot be transferred automatically to healthy-consumer products.*

1. The cognitive-health market has changed faster than cognitive-health science

For decades, the commercial language of cognitive nutrition was dominated by ageing. "Memory support" implicitly meant the older consumer, and product development consequently focused on age-associated memory complaints, cerebral circulation, antioxidant protection or ingredients traditionally associated with neurodegeneration. That demographic model is now incomplete.

A teenager switching continuously between educational platforms, social media, gaming and audiovisual stimuli may experience attentional fragmentation without having a cognitive disorder. A medical resident after a night shift, an engineer working across time zones, a university student during examinations, a perimenopausal executive with sleep disruption, and a 72-year-old with subjective memory complaints may all describe a similar consumer problem: concentration is poorer than expected and memory feels less efficient. Biologically, however, these are not the same problem.

The first principle of next-generation formulation should therefore be simple: a common cognitive complaint does not imply a common biological bottleneck. Improvements are also intrinsically difficult to demonstrate in healthy participants whose baseline performance is already high. In many real-world settings, preserving cognition under physiological stress may be more useful than creating a small increase in performance under ideal laboratory conditions.

The relevant question is consequently no longer "Does ingredient X improve cognition?" It is: "In whom, under which physiological state, against which cognitive bottleneck, over what time scale, and with what evidence of target engagement does ingredient X preserve or enhance performance?"

2. Cognitive performance is a dynamic state, not a fixed trait

Cognitive ability contains relatively stable components, but moment-to-moment performance varies substantially within the same person. Sleep duration, circadian phase, stress, hydration, dietary status, physical activity, environmental conditions, emotional state, hormonal state and preceding mental workload can all change performance.

The practical importance of this variability is increasing because it can now be measured outside the laboratory. Matias et al. (2026) followed 82 cognitively healthy adults for ten months using consumer wearables and mobile technologies. Passive behavioural, physiological and environmental data captured meaningful variability in cognitive and affective outcomes, although patient-reported outcomes were more predictable than performance-based cognition. This is not yet a validated nutritional decision system; it is evidence that everyday physiological context can be quantified at sufficient resolution to support longitudinal brain-health research.

Traditional parallel-group trials often collapse this variability into a baseline test and a single endpoint. That design can average away a state-dependent effect. Future trials should ask whether an intervention prevents deterioration on high-demand days, reduces within-person performance variability, preserves attention after insufficient sleep, accelerates post-load recovery, or benefits participants whose baseline biological status predicts lower reserve.

KEY DISTINCTION

Cognitive enhancement = performance above an individual's usual baseline. Cognitive resilience = reduced performance loss when a cognitive system is challenged. For many healthy populations, resilience may be the more plausible and ecologically relevant target.

3. Cognitive Load–Reserve Matching: a proposed framework

We propose **Cognitive Load–Reserve Matching (CLRM)** as a translational framework. It assumes that observed performance emerges from the interaction of relatively stable capacity, current task load, available physiological reserve, state disruptors, domain-specific demands and temporal alignment between intervention and challenge.

The model can be expressed heuristically as: functional cognitive performance = trait capacity + available reserve − current load − state-related impairment. This is not a validated quantitative equation. It is a testable conceptual model designed to predict where nutritional effects should be easiest to detect.

The central hypothesis is that the magnitude of a cognitive-nutrition effect should often increase as the biological process targeted by the intervention becomes more limiting. This offers a mechanistic explanation for why the same ingredient can look weak in rested, high-performing participants yet more informative under sleep loss, high cognitive demand, low nutrient status or metabolic vulnerability.

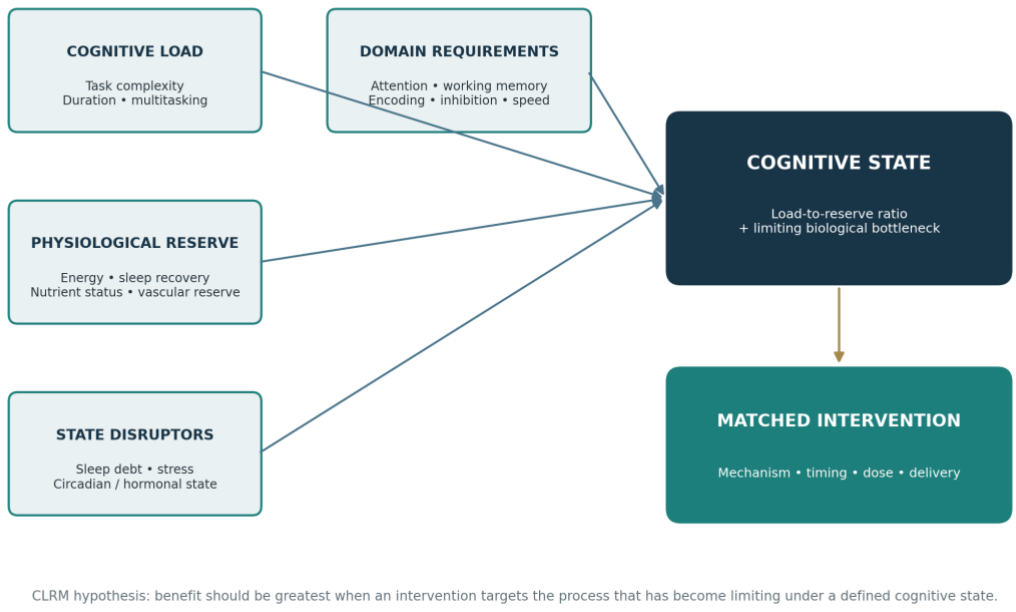

Figure 1. Cognitive Load–Reserve Matching (CLRM). Original conceptual model proposed in this article. It is intended to generate testable hypotheses rather than to imply validated clinical scoring.

4. Creatine illustrates state-dependent cognitive nutrition

Creatine is an unusually useful test case because the contrast between rested and stressed states is visible in controlled human experiments. In the largest preregistered double-blind crossover study to date, 123 participants received 5 g/day for six weeks; effects on the primary reasoning and working-memory outcomes were small and not statistically significant, although the authors considered some exploratory signals compatible with modest benefit (Sandkühler et al., 2023). A separate six-week dose-response trial in young adults likewise found no significant cognitive improvement (Moriarty et al., 2023).

The physiological context changed dramatically in the sleep-deprivation experiment by Gordji-Nejad et al. (2024). During approximately 21 hours of sleep deprivation, a single high experimental dose of creatine monohydrate altered cerebral high-energy phosphate measures and attenuated fatigue-related cognitive deterioration, with improvements in processing-related performance. The dose used - 0.35 g/kg - was experimental and should not be converted into a routine consumer recommendation. Its scientific value lies elsewhere: neural energetic demand appears capable of changing the functional relevance of substrate availability.

This pattern supports a stronger positioning of creatine as a candidate for cerebral energetic resilience research than as a universal intelligence enhancer. Future work should focus on defined high-demand states, habitual dietary creatine exposure, sleep debt, shift work, and populations in which brain-energy reserve may be altered.

5. Adolescence: an underdeveloped cognitive-nutrition window

Adolescence should not be treated as a smaller version of adulthood. Executive control, inhibitory processing and emotion regulation continue to mature while academic load, screen exposure and insufficient sleep may increase. This combination creates a high-demand population in which the ethical priority should be nutritional adequacy and resilience rather than stimulant escalation.

A particularly instructive development appeared in 2026. Lopresti and Smith studied 82 teenagers aged 13–18 years with more than four hours/day of screen exposure and low fruit and vegetable intake. Six months of lutein 10 mg plus zeaxanthin 2 mg increased macular pigment optical density (MPOD) versus placebo and improved tests of attention and processing speed, while not improving visual reasoning, non-verbal memory, gaming performance, self-reported attention or sleep (Lopresti & Smith, 2026). The study was sponsor-funded, which should remain part of the evidence appraisal, but the biomarker-plus-function design is scientifically valuable.

This finding builds on controlled work in younger adults and children. Renzi-Hammond et al. (2017) reported increases in MPOD and selected cognitive improvements after 12 months of lutein/zeaxanthin in healthy 18–30-year-olds. Parekh et al. (2024) reported MPOD, visual and cognitive signals in children aged 5–12 years after six months. The convergence suggests a researchable visual–cognitive axis: in high-screen populations, retinal physiology and cognitive efficiency may be better studied as a connected functional system than as separate “eye health” and “brain health” markets.

6. Omega interventions show why target engagement matters

Omega-3 research illustrates a recurring problem in nutritional cognition: administration is not equivalent to biological exposure. Trials often treat capsule assignment as the intervention variable while incompletely characterising baseline status or the magnitude of biological change.

Bell et al. (2026) randomised healthy 13–14-year-olds to a proprietary algae-derived omega blend or MCT placebo for 16 weeks. The Omega-3 Index increased only in the active group, demonstrating target engagement. The authors reported improvements in immediate and delayed word recall, attention-network reaction times and EEG measures. However, the full paper makes an important methodological point: several cognitive benefits were identified in post hoc analyses of main effects of time rather than robust treatment-related interactions. The study is therefore promising, especially because exposure was objectively confirmed, but it should not be overstated as definitive proof of broad cognitive enhancement.

This is precisely why next-generation trials need three linked layers: ingredient exposure → biological target engagement → functional outcome. For omega interventions, an Omega-3 Index is usually more informative than nominal compliance alone. For other mechanisms, equivalent biomarkers should be built into trial design whenever feasible.

A practical target-engagement architecture

Intervention concept	Target-engagement layer	Functional endpoint	Best research context
Lutein / zeaxanthin	Macular pigment optical density; serum carotenoids	Visual attention; processing speed	Development / high-screen
Omega fatty acids	Omega-3 Index	Memory; executive function	Development / low baseline status
Creatine	Cerebral creatine / phosphocreatine in mechanistic substudies	Resilience under sleep or load stress	High-demand / sleep debt
MCT / ketogenic substrate	β-hydroxybutyrate; ketone exposure	Memory / executive outcomes	Metabolic vulnerability / MCI
Sleep-directed intervention	Actigraphy / wearable sleep metrics	Next-day vigilance; working memory	Poor-sleep phenotype
Stress-directed intervention	HRV; cortisol where justified	Attention under stress; fatigue after load	Stress-sensitive phenotype

Table 2. Examples of target-engagement measures. Biomarkers should be selected for mechanistic relevance and validated analytical performance, not because they are convenient to collect.

7. Domain-specific effects may differ across generations

Citicoline illustrates how a common biochemical intervention may express differently across life stages. In 75 healthy adolescent males, 28 days of citicoline was associated with improved attention, psychomotor speed and lower impulsivity versus placebo (McGlade et al., 2019; first published online in 2015). The study was limited to males and used a branded ingredient, so generalisation should be restrained.

In a separate randomized trial of adults aged 50–85 with age-associated memory impairment, 500 mg/day for 12 weeks produced greater improvements in episodic and composite memory than placebo (Nakazaki et al., 2021). This study was sponsored by the ingredient manufacturer and included company-employed authors, an important conflict-of-interest consideration.

The useful inference is not that citicoline is universally effective. It is that membrane/cholinergic substrate support may manifest in different functional domains according to the dominant demand of the population. CLRM predicts that age should be treated as one variable among several, not as the formulation logic itself.

8. Acute attention is not synonymous with long-term brain health

Commercial cognitive products frequently conflate alertness, concentration, memory, learning and long-term brain health. These constructs are not interchangeable. Caffeine is the clearest example: acute adenosine antagonism can improve alertness and selected attentional measures, but that does not establish improved memory consolidation or long-horizon neuroprotection.

A 2025 systematic review and meta-analysis of randomized trials concluded that L-theanine plus caffeine and L-theanine alone can produce small-to-moderate effects on selected cognitive and mood outcomes, while confidence intervals frequently signalled substantial uncertainty regarding direction and magnitude (Payne et al., 2025). The appropriate interpretation is therefore domain- and time-specific, not “universal nootropic.”

This distinction is especially important in younger users. EFSA’s caffeine safety opinion provides exposure thresholds for healthy populations; it does not create a recommendation to formulate stimulant products for minors. Safety, efficacy, permitted claims and responsible product positioning are separate questions.

9. Flavonoid studies support challenge-sensitive testing

Wild-blueberry studies provide a useful methodological clue: effects can become more visible when the task itself is demanding. Whyte et al. (2017) used a modified attention network task in children aged 7–10 and reported faster performance after wild blueberry particularly on incongruent and high-load trials. Barfoot et al. (2019) found acute improvements in verbal memory and attentional executive-function measures, without improvement in reading outcomes.

At the other end of the age spectrum, six months of wild-blueberry powder improved processing speed relative to placebo in older adults with mild cognitive decline, accompanied by electrophysiological findings (Cheatham et al., 2023). These studies are heterogeneous and do not prove a single mechanism across ages. What they do support is the need to avoid tests that are too easy to expose reserve limitations.

10. Negative nootropic trials are scientifically valuable

A rigorous field cannot be built from positive ingredients alone. Lopresti and Smith (2025) tested 300 mg/day of a Bacopa monnieri extract for 12 weeks in adults with self-reported memory and attention problems. There were no between-group improvements in the primary outcomes of verbal learning, attention or working memory. Greater reductions occurred in self-reported stress reactivity and in fatigue/stress after a demanding cognitive task.

The result should not be reduced to “Bacopa does not work.” A better translational interpretation is that the tested preparation may have been more relevant to stress/fatigue modulation than to direct enhancement of the primary cognitive endpoints. If replicated, that would reposition the research question toward a stress-sensitive cognitive phenotype rather than a generic memory claim.

11. Recovery may be a more important cognitive target than continuous stimulation

Poor sleep impairs attention, working memory, executive control, learning and memory consolidation. A product that extends daytime alertness but worsens subsequent sleep may improve one performance window while degrading the next day's reserve. This creates a case for biphasic cognitive nutrition: performance support during predictable demand, followed by recovery support that does not perpetuate stimulation into the biological night.

Magnesium L-threonate is a useful example of both opportunity and evidential caution. Hausenblas et al. (2024) reported improvements in several subjective and wearable-derived sleep/daytime measures in adults with self-reported sleep problems; a corrigendum was later published. A subsequent randomized trial by Lopresti and Smith, published in January 2026, reported a modest advantage over placebo on the NIH Cognitive Toolbox composite and selected memory/reaction-time measures after six weeks, while placebo also improved substantially and several sleep endpoints were negative. Both branded-intervention studies require independent replication before strong product-level conclusions are justified.

The broader hypothesis remains testable: in poor sleepers, improving recovery physiology may yield greater next-day cognitive benefit than simply increasing daytime stimulation.

12. Midlife women should become a distinct research population

Pooling men and women across broad adult age ranges can obscure a major physiological transition. An updated systematic review and meta-analysis published in 2026 included 26 articles and 9,428 participants and found evidence of cognitive differences during perimenopause, while also highlighting substantial methodological variability in staging and outcome selection (Bangle et al., 2026).

This population is particularly informative for CLRM because sleep disturbance, vasomotor symptoms, stress, reproductive-stage changes and metabolic shifts can coexist. A generic "women 40+" supplement is therefore a weak scientific construct. Trials should classify reproductive stage rigorously and stratify by symptom phenotype, sleep quality and metabolic context.

A high-value research programme would test whether sleep-dominant, stress-dominant and metabolic-vulnerability phenotypes respond differently to energy-resilience, membrane-support or recovery-directed interventions. Chronological age alone is unlikely to explain the response variance.

13. In older adults, the frontier may be metabolic rescue rather than generic stimulation

In ageing and mild cognitive impairment, an increasingly interesting line of research concerns cerebral fuel flexibility. MCT-derived ketones can provide an alternative oxidative substrate when glucose utilisation is constrained. This mechanism should not be generalized to every healthy older adult, but it creates a mechanistically coherent target for metabolically vulnerable phenotypes.

Duan et al. (2025) randomised 280 older adults with MCI to placebo, MCT, DHA or MCT+DHA for 12 months. All three active groups showed improvements on reported cognitive measures versus placebo alongside changes in total ketone bodies and mitochondrial-related markers; the combined intervention showed several stronger effects. Because the population had clinically defined MCI, these findings cannot be translated directly into claims for healthy consumers. They do, however, reinforce a research paradigm in which cognition may be supported by supplying an alternative substrate when the preferred energetic pathway is constrained.

This distinction - stimulation versus metabolic rescue - is likely to become increasingly important as cognitive nutrition becomes more mechanistic.

14. From ingredient stacks to functional architectures

Most cognitive supplements are still ingredient inventories. A more rigorous formulation process starts from a phenotype and asks which biological systems must be supported simultaneously without redundancy, under-dosing or mechanistic contradiction.

We propose five research modules: neural energy resilience; membrane and neurotransmitter-substrate availability; sensory–neural efficiency; stress and recovery regulation; and neurovascular/phytochemical support. Ingredients should enter a formulation only when they have a defined role inside an architecture and a dose compatible with the evidence base.

A small 2026 randomized study in children with ADHD or significant subthreshold symptoms reported stronger attention and inhibition improvements with a higher-dose phosphatidylserine plus DHA formulation than comparator formulations (Jaicks & Kinter, 2026). The sample was only 45 children and the population was clinical; replication is essential. Nevertheless, it illustrates why dose, co-formulation and phenotype matter more than simply listing phosphatidylserine or DHA on a label.

Functional module	Candidate research inputs	Best-fit context	Validation logic
Neural energy resilience	Creatine; ketogenic/MCT strategies in selected phenotypes	Sleep debt; prolonged load; metabolic vulnerability	Mechanistic target engagement + challenge testing
Membrane / substrate support	Citicoline; DHA; phosphatidylserine	Attention, signalling, memory encoding	Baseline status + domain-specific cognition
Sensory–neural efficiency	Lutein; zeaxanthin	High screen/visual demand	MPOD + attention/processing speed
Stress / recovery regulation	Theanine; magnesium in selected phenotypes; other validated stress modulators	Stress-sensitive cognition; poor sleep	HRV/sleep/cortisol where justified + next-day performance
Neurovascular / phytochemical support	Anthocyanin-rich foods/extracts and other validated vascular bioactives	High task demand; ageing	Task-demand manipulation + vascular/mechanistic measures

Table 3. Functional formulation architecture. Candidate inputs are research examples, not universal recommendations and not a substitute for product-specific safety, regulatory and dose assessment.

15. Chronocognitive nutrition: formulation in time, not only in composition

Conventional supplements assume that all active compounds should reach the consumer simultaneously. Neurobiology offers little reason for that assumption. Cognitive demand varies throughout the day, while stimulation, substrate support, membrane accretion and recovery operate on different time scales.

We therefore propose chronocognitive nutrition as a research concept with four temporal layers: an immediate-response layer for acute attentional demand; a sustained-resilience layer for several hours of substrate or physiological support; an adaptive-recovery layer designed not to extend stimulation into the biological night; and a long-horizon layer for slowly changing variables such as membrane composition or tissue carotenoid status.

The resulting product system may be a platform rather than a single capsule: a daily foundation plus event-specific or time-specific formats. The innovation is temporal matching, not dosage-form novelty for its own sake.

16. Cognitive nutrition should become closed-loop

Current supplements operate open-loop: take the product and hope that cognition improves. Wearables and smartphone microtasks create the possibility of a different architecture: measure state → infer probable bottleneck → select intervention → measure response → update the model.

The 2026 wearable study by Matias et al. does not validate such a nutritional loop, but it demonstrates that passive multimodal data can capture within-person variation relevant to brain health. A future system could combine sleep duration, timing, HRV, activity, light exposure, subjective stress and a short psychomotor or working-memory task before determining whether an acute cognitive intervention is even indicated.

This should be developed experimentally and conservatively. Algorithms must not convert imperfect consumer sensors into pseudo-diagnostic claims. The research opportunity is to use repeated state measurement to improve trial sensitivity and individual response modelling.

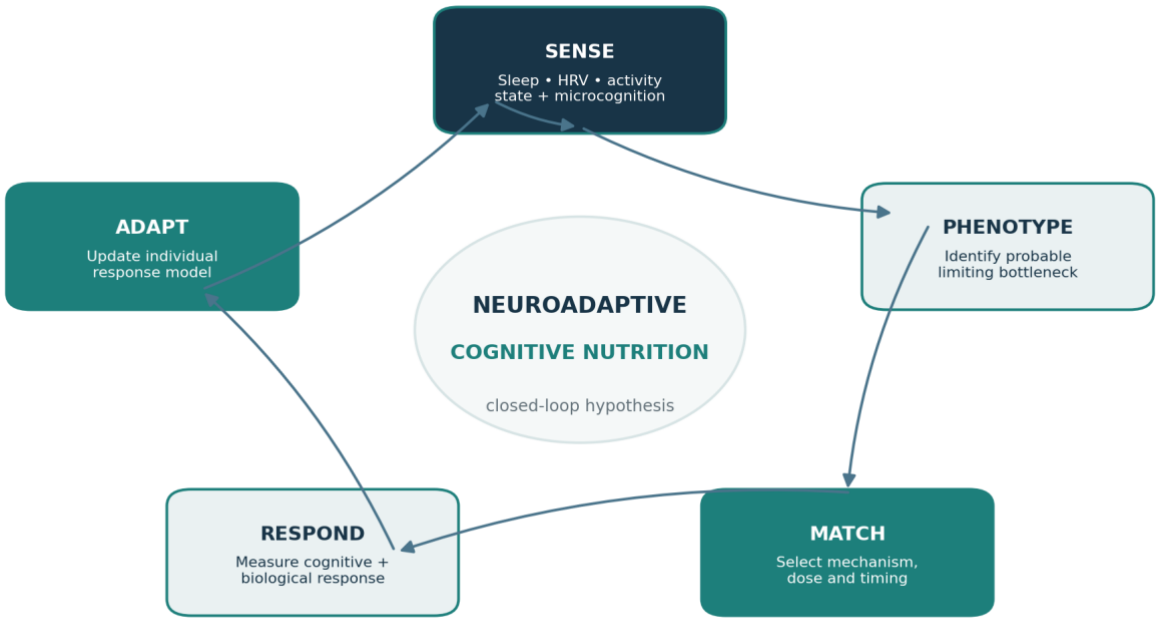

Figure 2. Closed-loop neuroadaptive cognitive nutrition. Original research concept: sensing, phenotyping, intervention matching and response learning form a repeated loop rather than a fixed daily prescription.

17. The cognitive digital twin: a testable long-term frontier

A more ambitious extension would be an individual cognitive digital twin - not a full simulation of the brain, but a probabilistic model of expected performance under recurring physiological states. A baseline observation period could integrate sleep, HRV, activity, light exposure, caffeine use, diet, stress, screen exposure, reproductive stage when relevant, and repeated 2–3 minute cognitive tasks.

The model would estimate the person's expected performance under a given state. Intervention success would then be expressed as deviation from that personalised expected trajectory rather than only as a group-average endpoint: did performance exceed what would normally be expected for this individual after this amount of sleep, at this circadian time and under this workload?

This is currently a research proposal. It raises substantial questions of validation, bias, privacy, data governance and explainability. Precisely because of those limitations, it should be developed first as a research instrument rather than a consumer-facing diagnostic system.

18. Formulating across generations without formulating by generation

The paradoxical conclusion is that serving multiple generations may require less reliance on age bands. Age remains relevant because physiology changes through life, but the operational formulation variable should increasingly be the functional phenotype: developing attention, digital/visual load, high-load performance, sleep debt, stress-sensitive cognition, midlife transition, metabolic vulnerability, healthy longevity or clinically defined decline.

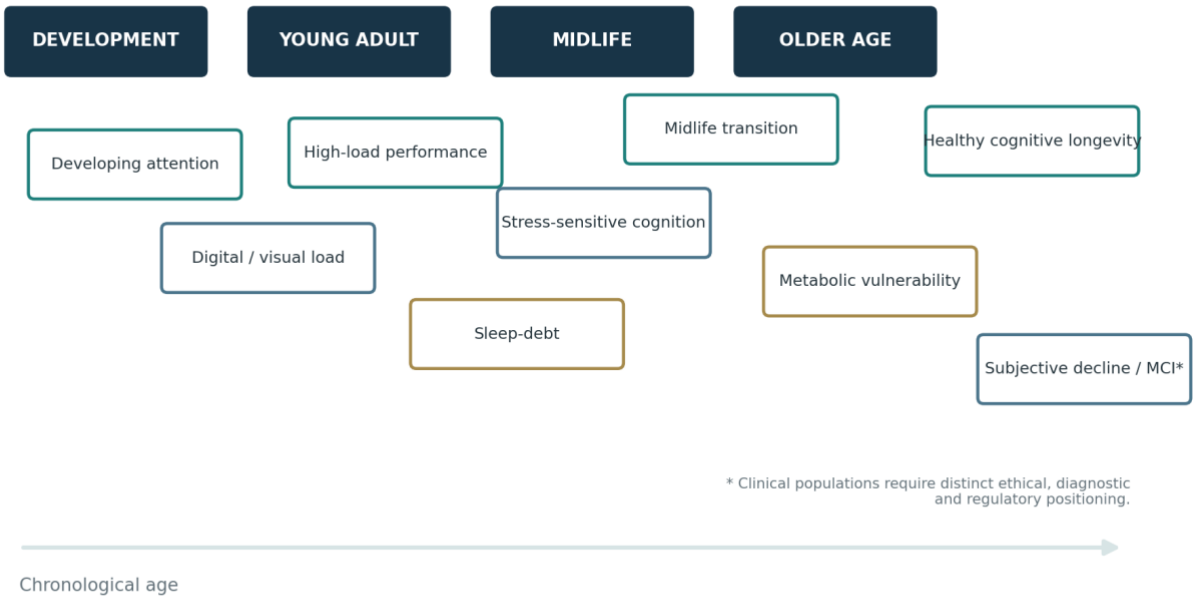

Figure 3. Phenotype map across the lifespan. The same functional phenotype can occur at more than one chronological age, while different mechanisms may dominate within the same age group.

19. Challenge-based clinical validation

Healthy-population cognition trials often suffer from ceiling effects. A challenge model exposes reserve. Suitable experimental stressors can include prolonged cognitive testing, controlled distraction, multitasking, partial sleep restriction, time-on-task fatigue, high visual load, postprandial metabolic challenge or standardized psychosocial stress - each selected because it maps to the proposed mechanism.

The logic resembles cardiovascular stress testing: normal function at rest does not prove adequate reserve during demand. Cognitive nutrition should increasingly ask how much performance is lost under a controlled challenge and whether the intervention reduces that loss.

This approach also improves falsifiability. If an energy-resilience formulation does not attenuate decline under a validated energetic or sleep challenge, the mechanistic proposition has failed more informatively than if a low-demand memory test simply shows no change.

20. From mean treatment effects to responder biology

Average treatment effects can conceal biologically meaningful heterogeneity. A near-zero mean may contain strong responders, non-responders and participants who were never biologically deficient in the targeted pathway.

Future trials should prospectively evaluate effect modification by baseline nutrient status, habitual diet, sex, reproductive stage, sleep quality, habitual caffeine exposure, stress, chronotype, metabolic phenotype, baseline cognition and - where justified - genetic or microbiome variables. These analyses should be prespecified whenever possible; otherwise they risk becoming post hoc storytelling.

Precision nutrition and cognitive neuroscience converge here: the objective is not to manufacture responder subgroups after the fact, but to identify mechanistically credible predictors before the intervention begins.

21. Target engagement should become a minimum standard

A negative cognitive trial is uninterpretable if the intended biological target was never engaged. Failure may reflect a wrong mechanism, inadequate dose, poor delivery, high baseline status, inadequate tissue exposure,

insensitive cognitive testing, insufficient challenge, inappropriate duration or a mechanism that simply does not matter functionally. Biomarkers cannot solve every ambiguity, but they can separate several of these explanations.

DEVELOPMENT SEQUENCE

Phenotype → limiting bottleneck → mechanism → ingredient/intervention → dose → delivery → target-engagement biomarker → cognitive endpoint → real-world relevance.

22. The end of the "kitchen-sink nootropic"

The scientific future is unlikely to belong to formulas containing twenty recognised ingredients at sub-evidential doses. Such products make efficacy attribution nearly impossible, increase the probability of under-dosing and interaction, complicate regulatory assessment and prevent meaningful responder analysis.

A stronger product may contain fewer ingredients but possess a transparent biological rationale, adequate dose, compatible kinetics and a validation pathway that can actually determine whether the intended mechanism was reached.

23. A proposed evidence hierarchy for cognitive interventions

Level 1	**Biological plausibility**	Mechanism supported by credible experimental evidence.
Level 2	**Human target engagement**	The intervention changes the intended biological variable in humans.
Level 3	**Domain-specific cognitive effect**	Controlled evidence for a defined cognitive function.
Level 4	**Context replication**	The effect is reproduced under the real-world state for which the product is intended.
Level 5	**Ecological validity**	The intervention preserves or improves meaningful everyday cognitive performance.

Table 4. Proposed translational evidence hierarchy. It is a framework for R&D prioritisation, not a regulatory grading system.

24. Four applied research platforms

Platform A — Digital resilience in adolescents

Healthy adolescents with high screen exposure. Prioritise non-stimulant strategies, objective screen/sleep characterization, MPOD and/or nutrient-status biomarkers, and attention/inhibitory-control tasks. Test whether benefit is concentrated in participants with low baseline nutrient status and high visual-cognitive load.

Platform B — Cognitive resilience under sleep debt

Healthy young and middle-aged adults under controlled partial sleep restriction or validated naturalistic sleep debt. Primary endpoint: performance loss relative to rested baseline. Mechanistic substudies can test energetic target engagement where feasible.

Platform C — Perimenopausal cognitive resilience

Women classified using accepted reproductive-stage criteria and stratified by sleep, vasomotor, stress and metabolic phenotype. Prioritise verbal learning, working memory, attention, reaction-time variability and recovery metrics.

Platform D — Metabolic cognitive ageing

Separate cognitively healthy older adults, subjective cognitive decline and clinically defined MCI. Test membrane, energetic and vascular strategies with strict population-specific claims and mechanistic biomarkers.

25. Ten hypotheses for the next five years

H1 — State-dependent efficacy	Effects will be larger during defined physiological or cognitive stress than during rested baseline testing.
H2 — Bottleneck specificity	Response magnitude will correlate with baseline impairment in the pathway targeted by the intervention.
H3 — Biomarker-response coupling	Mechanism-specific biomarker change will predict functional response better than nominal supplement assignment alone.
H4 — Variability reduction	Some interventions will reduce day-to-day intra-individual cognitive variability even when mean performance changes little.
H5 — Visual–cognitive coupling	In high-screen populations, improvements in visual-system biomarkers will predict selected attention and processing-speed outcomes.
H6 — Recovery-mediated cognition	Poor sleepers will gain more from recovery-directed interventions than from additional stimulation alone.
H7 — Reproductive-stage precision	Among midlife women, reproductive and symptom phenotype will explain more response variance than chronological age.
H8 — Metabolic rescue	Alternative energetic substrates will preferentially benefit individuals with metabolic vulnerability rather than metabolically healthy high performers.
H9 — Chronocognitive superiority	Time-separated performance and recovery strategies will outperform indiscriminate all-day stimulation for sustained function.
H10 — Closed-loop superiority	Adaptive interventions informed by recent physiological and cognitive data will improve resilience more than fixed daily supplementation in appropriately validated systems.

Table 5. Prospective hypotheses generated by the CLRM framework. None should be interpreted as established efficacy statements before prospective testing.

26. Regulatory and ethical boundaries

Innovation in cognitive nutrition must remain disciplined. Foods and food supplements cannot drift conceptually into unlicensed treatment of ADHD, dementia, depression, sleep disorders or other medical conditions. Evidence derived from clinical populations can generate hypotheses; it cannot automatically substantiate consumer claims in healthy populations.

In the European Union, nutrition and health claims are governed by Regulation (EC) No 1924/2006 and must comply with authorised wording and conditions of use. Scientific plausibility, publication evidence, legal claim authorisation and promotional language are distinct layers. The more sophisticated the research platform becomes, the more important that separation will be.

The same restraint applies to digital phenotyping. Wearable-derived readiness or cognition estimates should not be represented as diagnoses unless they have been validated and regulated for that purpose. Data minimisation, consent, security, algorithmic transparency and the right not to be continuously profiled should be treated as design requirements, not afterthoughts.

27. Conclusion: from “brain boosters” to neuroadaptive nutrition

The expanding demand for memory and focus across generations should not lead to an indiscriminate expansion of the traditional nootropic category. It should force the field to become more precise.

The adolescent does not need an anti-ageing brain supplement. The exhausted professional does not necessarily need stronger stimulation. The perimenopausal woman should not be treated as a generic middle-aged consumer. The healthy older adult and the person with mild cognitive impairment should not be placed in the

same experimental category. And an intervention that fails to increase cognition in a rested, nutritionally replete participant may still be valuable if it preserves performance when a specific reserve is challenged.

The emerging opportunity is neuroadaptive nutrition: systems designed around the limiting biological process at the moment cognitive demand exceeds available reserve. That requires better phenotyping, fewer arbitrary ingredient stacks, stronger target-engagement measurements, challenge-based trials, longitudinal digital measurement and a disciplined distinction between enhancement, resilience and disease treatment.

The future cognitive product may therefore be defined less by the number of compounds inside the capsule than by the quality of the physiological question it was designed to answer. Memory and focus are not single targets. They are emergent functions of a dynamic biological system. Cognitive nutrition should be designed accordingly.

SCIENTIFIC STATUS & DISCLOSURE

CLRM, chronocognitive nutrition, closed-loop neuroadaptive nutrition and the cognitive digital twin are conceptual frameworks advanced by the author in this Perspective. They require prospective validation. This article is not medical advice and does not establish product-specific efficacy, safety or legal claim authorisation. Several cited trials used proprietary ingredients or had industry sponsorship; those limitations are identified where materially relevant.

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Editorial note

This publication is designed as a scientifically grounded frontier article rather than a systematic review or clinical guideline. The literature set is selective and mechanism-driven. A subsequent academic paper should expand the search strategy, risk-of-bias analysis, evidence tables, preregisterable hypotheses, statistical framework and formal methods necessary for peer-reviewed submission.