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bounce matters

CLINICAL WEBINAR

Optimising Brain Energy, Mood and Cognitive Resilience: Evidence-Based Nutraceutical Strategies

Presented by:
Jo Grabyn, Nutritional Medicine Practitioner

Presenter | Jo Grabyn

Jo Grabyn BHSc (Nutritional Medicine)

1 Brain 1 Body for Life

Jo Grabyn is a highly experienced Nutritional Medicine Practitioner specialising in brain optimisation and the prevention and reversal of cognitive decline. Driven by a commitment to understanding how the brain can be protected and restored, she has spent over a decade supporting patients in clinical practice.

Jo was part of the inaugural practitioner cohort trained by Dr Dale Bredesen at the Buck Institute for Research on Aging and has undertaken advanced training with leading international experts, including Dr Daniel Amen, Dr James Greenblatt, and Dr Dayan Goodenowe.

She now delivers vital practitioner training and masterclasses designed to equip clinicians with practical, life-changing strategies.

Host | Tulsi Ryan

Tulsi Ryan is a Health Educator at Designs for Health, with over 15 years of experience in the natural health industry. In her role, she provides practitioners with evidence-based education and clinical insights, with a strong focus on translating complex scientific concepts into practical strategies for patient care.

For more than eight years, Tulsi has worked closely with practitioners across Australia, delivering expert guidance on both clinical applications and product education. Her professional interests include gut health and the gut–brain connection, women's health, sports nutrition, and body composition.

Tulsi is passionate about sharing her knowledge and industry insights in a way that supports and empowers practitioners, helping them feel confident and capable in their clinical decision-making.

Webinar Overview

Six learning objectives for evidence-based nutraceutical practice:

1. **Brain bioenergetics –** Mitochondrial ATP & NAD metabolism
2. **Drivers of cognitive symptoms –** Brain fog, fatigue and dysfunction
3. **Evidence-based nutraceuticals –** Mechanisms, dosing & clinical use
4. **Hormonal transitions & the brain –** Menopause & neurometabolism
5. **Layered clinical strategy –** Personalised nutraceutical protocols
6. **Nutraceutical quality assessment –** Standardisation, bioavailability & evidence

Why This Matters Now

Brain fog, fatigue, low mood → increasingly common

Younger patients presenting earlier

Traditional model = symptom management

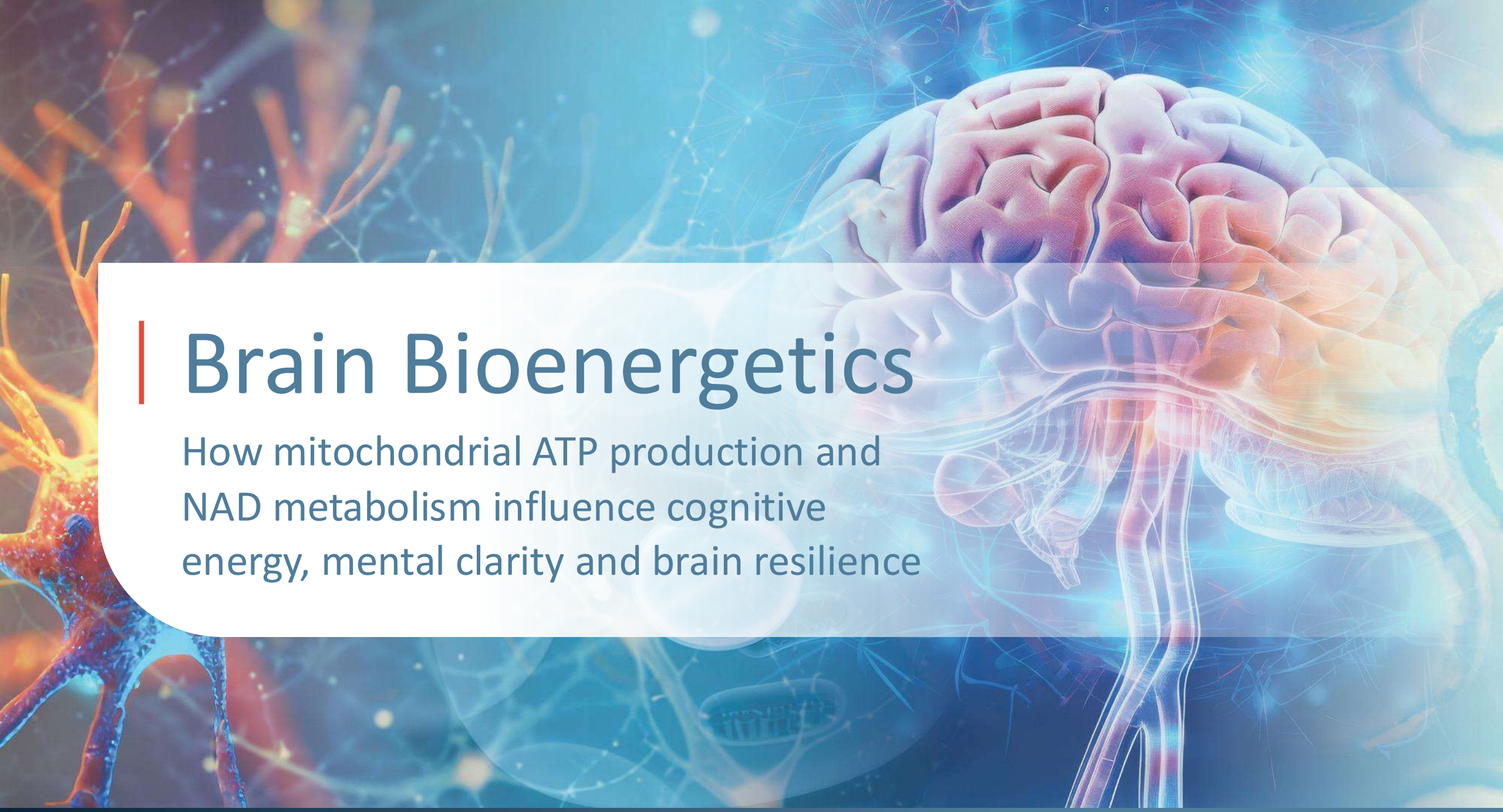
Missing piece = brain energy

A Different Lens

Brain symptoms are often metabolic

Energy → drives function

Function → drives symptoms



Brain Bioenergetics

How mitochondrial ATP production and NAD metabolism influence cognitive energy, mental clarity and brain resilience

The Brain's Extraordinary Energy Demand

20%
of body's energy consumed by the brain

2%
of total body weight

~86B
neurons requiring constant ATP

10x
higher metabolic rate vs resting muscle

- The brain runs almost exclusively on glucose, converted to ATP via mitochondrial oxidative phosphorylation
- Neurons cannot store significant energy reserves — continuous mitochondrial function is essential
- Even brief disruptions to ATP synthesis impair synaptic signalling and neurotransmitter production
- Cognitive tasks significantly increase regional cerebral metabolic rate, demanding flexible bioenergetic capacity

Mitochondria: The Brain's Power Plants

1. Glycolysis

Glucose → Pyruvate in cytoplasm
(2 ATP net)

2. Krebs cycle

Pyruvate → Acetyl-CoA → electron carriers
(NADH, $FADH_2$)

3. Electron Transport train

$NADH/FADH_2$ → electrochemical gradient
→ 32–34 ATP

4. ATP Synthase

Proton gradient drives ATP production
via Complex V

Neurons are mitochondria-dense

up to 2,000 mitochondria per neuron- highest density of any cell type

Location matters

mitochondria cluster at synapses where ATP demand is greatest during signalling

Dynamic network

mitochondria undergo constant fusion/fission to meet changing energy needs

NAD^+ Metabolism: The Master Regulator

NAD^+ (nicotinamide adenine dinucleotide) is essential for mitochondrial function, DNA repair, and cellular ageing

Energy Metabolism

- Electron carrier in glycolysis
- Critical for Krebs cycle
- Required for ETC function
- Drives ATP synthase activity

Cellular Repair

- Substrate for PARP enzymes
- Essential for DNA strand repair
- Activates sirtuins (SIRT1-7)
- Regulates epigenetic maintenance

Ageing & Decline

- **NAD^+ declines ~50% by age 50**
- Correlates with cognitive decline
- Reduced mitochondrial biogenesis
- Impaired stress resistance

ATP Availability & Cognitive Function

How mitochondrial output directly shapes our thinking, memory and mental speed

- **Synaptic Transmission**

  Action potentials require Na^+/K^+-ATPase pumps — directly ATP-dependent; low ATP = impaired signal propagation

- **Neurotransmitters Synthesis**

  Dopamine, serotonin, acetylcholine synthesis are energy-intensive processes requiring mitochondrial co-factors

- **Memory Consolidation**

  Long-term potentiation (LTP) demands sustained ATP for protein synthesis and synaptic remodelling

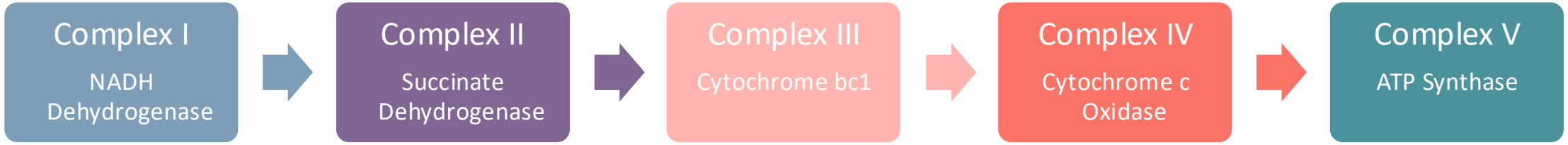
- **Executive Function**

  Prefrontal cortex has highest metabolic demand — particularly vulnerable to bioenergetic insufficiency

- **Mental Processing Speed**

  Myelin maintenance and axonal conduction velocity depend on continuous mitochondrial ATP output

Oxidative Phosphorylation & Electron Transport Chain



→ Proton (H^+) gradient drives ATP synthesis

- **ROS production**

  1–2% of electrons leak from the ETC, generating reactive oxygen species — a normal byproduct that becomes damaging under dysfunction

- **Co-factor dependency**

  1–2% of electrons leak from the ETC, generating reactive oxygen species — a normal byproduct that becomes damaging under dysfunction

- **Mitochondrial membrane potential (ΔΨm)**

  The proton gradient across the inner mitochondrial membrane drives ATP synthesis — collapse impairs all energy-dependent processes

- **Cognitive vulnerability**

  The brain's high oxygen consumption makes it particularly sensitive to ETC dysfunction and oxidative damage

Bioenergetic Resilience & Cognitive Reserve

Brain resilience depends on mitochondrial flexibility — the ability to switch fuel sources and adapt to metabolic stress

- **Mitochondrial Biogenesis**

  PGC-1α pathway drives formation of new mitochondria; upregulated by exercise, fasting, cold exposure, and certain nutraceuticals

- **Antioxidant Defence**

  Glutathione, superoxide dismutase, and catalase neutralise ETC-derived ROS — essential for maintaining mitochondrial integrity

- **AMPK Signalling**

  Energy sensor AMPK activates mitophagy (removal of damaged mitochondria) and promotes efficient ATP utilization

- **Ketone Utilisation**

  In glucose insufficiency, ketone bodies (BHB) can supply up to 60–70% of brain energy — an important resilience mechanism

- **Metabolic Flexibility**

  Ability to efficiently switch between glucose and fatty acid/ketone oxidation confers protection against cognitive decline

- **NAD^+/NADH Ratio**

  A high NAD^+:NADH ratio drives efficient ETC function; declining ratio is an early marker of metabolic ageing

Section 1 — Key Takeaways

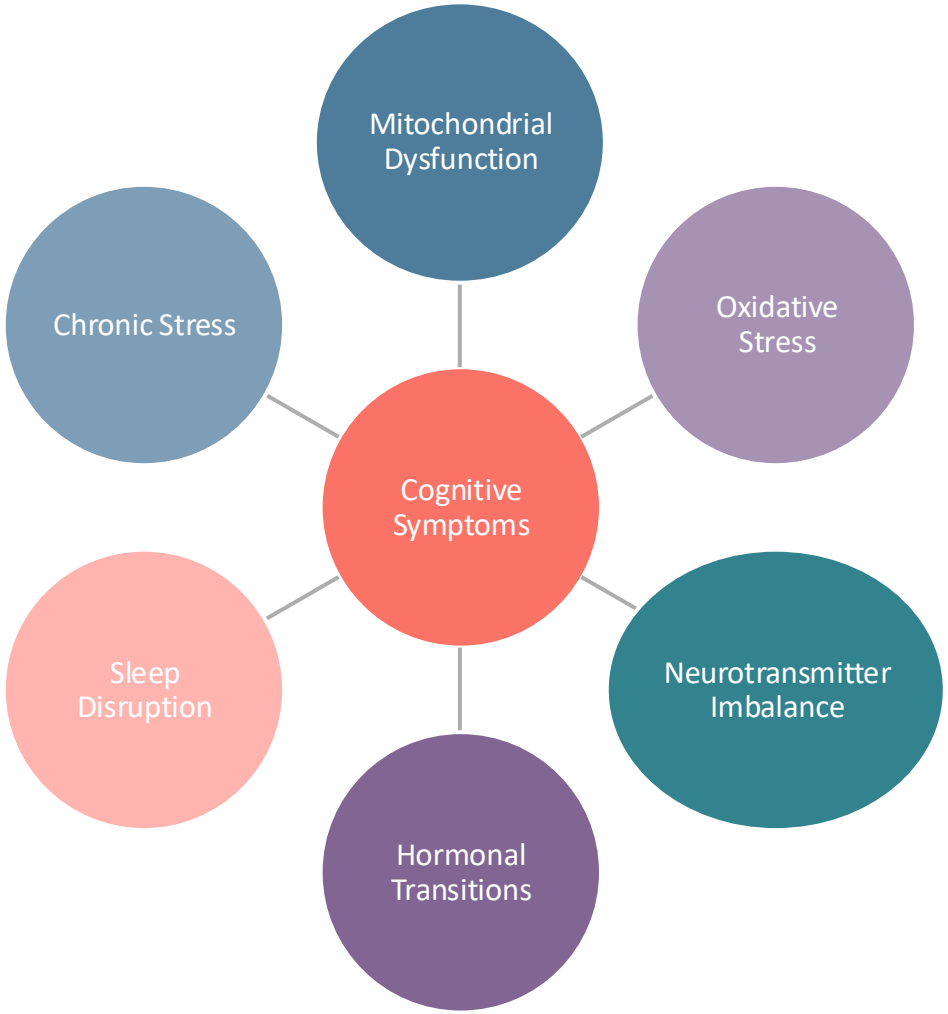
1. The brain consumes ~20% of the body's energy despite being only 2% of body weight — making it uniquely vulnerable to bioenergetic failure
2. Mitochondrial ATP production underpins every aspect of cognition, from synaptic firing to memory consolidation
3. NAD^+ is a master regulator of mitochondrial function and cellular repair — declining with age and chronic stress
4. The electron transport chain is the primary site of ATP generation and a key source of reactive oxygen species
5. Bioenergetic resilience — mitochondrial flexibility, biogenesis, and antioxidant defence — is central to cognitive reserve
6. Supporting mitochondrial health is a foundational strategy in nutraceutical approaches to cognitive performance

Drivers of Cognitive Symptoms

Recognising key physiological contributors to brain fog, fatigue and cognitive dysfunction

The Multifactorial Nature of Cognitive Decline

Brain fog, fatigue and cognitive dysfunction rarely arise from a single cause — a web of interconnected physiological disruptions.



Mitochondrial Dysfunction & Brain Fog

- **Reduced ATP output**
  → Insufficient energy for synaptic signalling
  → slowed processing, poor concentration
- **Impaired calcium buffering**
  → Dysregulated neuronal excitability
  → inconsistent mood and focus
- **Elevated reactive oxygen species**
  → Oxidative damage to membranes, proteins, and DNA → accelerated neuronal ageing
- **Mitochondrial membrane collapse**
  → Triggers apoptotic pathways
  → neuronal loss in key cognitive areas
- **Defective mitophagy**
  → Accumulation of dysfunctional mitochondria
  → chronic low-grade inflammatory signalling

Oxidative Stress & Neuroinflammation

The brain is especially vulnerable to oxidative damage due to its high oxygen consumption, lipid-rich membranes, and relatively modest antioxidant capacity

Sources of Brain ROS

- Mitochondrial electron leakage (ETC)
- NADPH oxidase activation (microglial)
- Xanthine oxidase activity
- Excitotoxic calcium overload

Consequences of Oxidative Damage

- Lipid peroxidation of neuronal membranes
- Lipid peroxidation of neuronal membranes
- DNA/RNA oxidation (8-OHdG marker)
- Mitochondrial genome damage

Neuroinflammation Loop

ROS activates NF-κB → pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) → microglial activation → more ROS → cycle perpetuates

Cognitive Impact

Chronic neuroinflammation disrupts hippocampal LTP, **reduces BDNF**, impairs glutamate recycling — directly impairing learning and memory

Neurotransmitter Imbalance & Cognitive Symptoms

Neurotransmitter	Role	Low State Symptoms	Depletion Drivers
Dopamine	Motivation, reward, attention, working memory	**Apathy, poor focus, low motivation, brain fog**	Chronic stress, poor sleep, nutritional deficiency
Serotonin	Mood regulation, emotional resilience, sleep onset	**Anxiety, irritability, rumination, insomnia**	Stress, gut dysbiosis, low tryptophan intake
Acetylcholine	Memory encoding, learning, attention	**Memory lapses, confusion, reduced learning speed**	Ageing, cholinergic deficit, anticholinergic meds
GABA	Inhibitory calm, stress modulation, sleep quality	**Anxiety, restlessness, poor sleep architecture**	Chronic stress, magnesium deficiency, HPA dysregulation
Noradrenaline	Alertness, arousal, stress response	**Mental fatigue, poor concentration, mood instability**	Prolonged stress, adrenal dysregulation

Chronic Stress & HPA Axis Dysregulation

Prolonged stress chronically elevates cortisol- progressively damaging the brain regions most critical for cognition

Acute Stress (Adaptive)

- Cortisol boosts attention & alertness
- CRH → ACTH → cortisol cascade
- Beneficial short-term cognitive enhancement
- Hippocampal LTP briefly upregulated

Chronic Stress (Maladaptive)

- Sustained high cortisol becomes neurotoxic
- Hippocampal neurogenesis suppressed
- Glutamate excitotoxicity increases
- HPA axis feedback dysregulated

Cognitive Consequences

- Working memory impairment
- Emotional dysregulation (amygdala hyper-reactivity)
- Reduced cognitive flexibility
- ↑ Risk of depression & anxiety

Sleep Disruption & Cognitive Impairment

Sleep is not passive recovery — it is when the brain consolidates memory, clears metabolic waste, and rebalances neurotransmitters

- **Glymphatic System**

  During deep sleep, glymphatic flow increases 10-fold — clearing amyloid-β, tau and other neurotoxic waste products

- **Memory Consolidation**

  Slow-wave sleep and REM are critical for converting short-term memories to long-term storage via hippocampal replay

- **Neurotransmitter Restoration**

  Sleep restores dopamine receptors, normalises serotonin synthesis, and replenishes acetylcholine pools

Effects of Chronic Sleep Loss

↓ Executive function

↓ Attention & reaction time

↑ Amyloid-β accumulation

↑ Neuroinflammatory markers

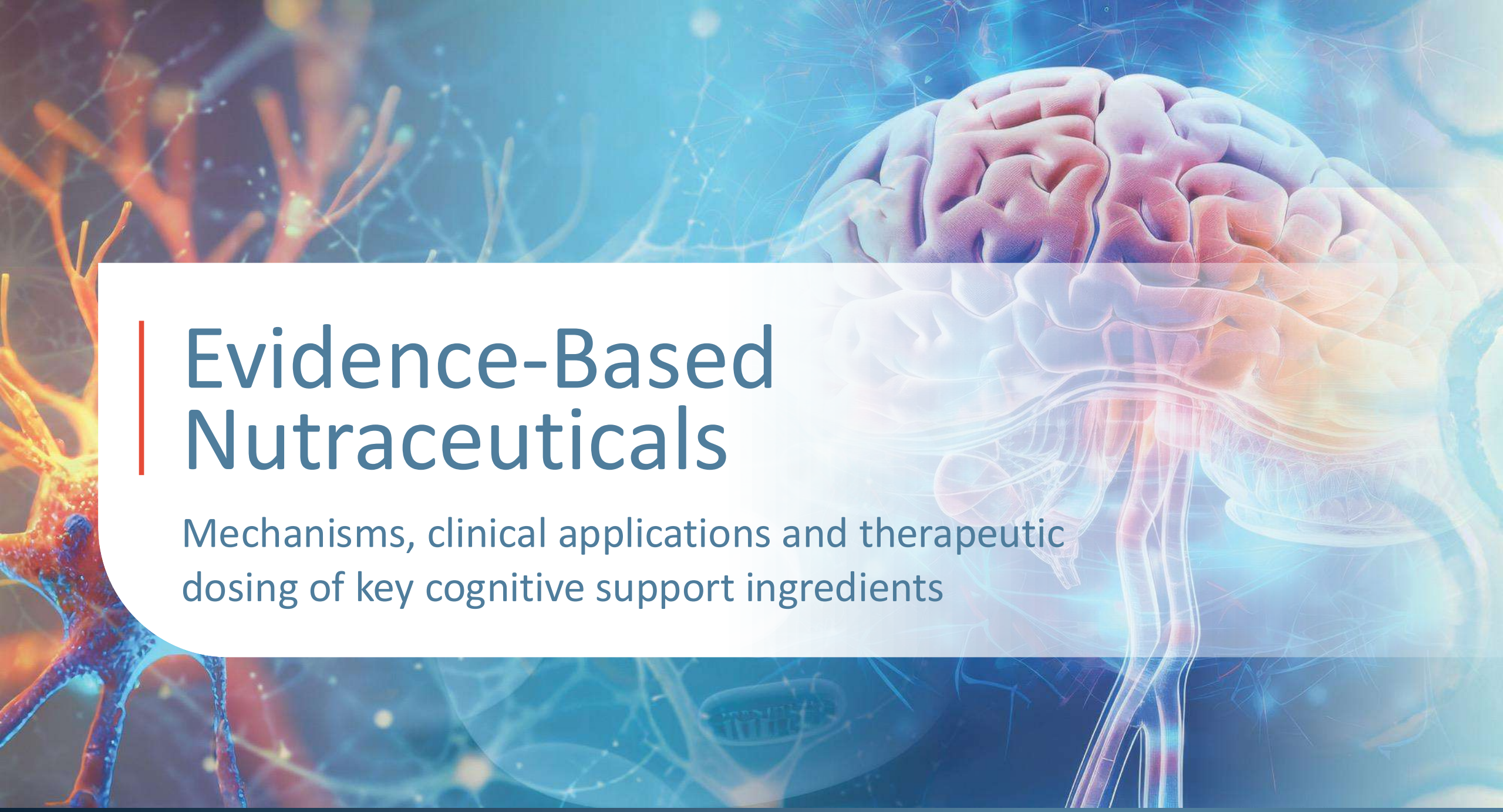
↓ Emotional regulation

↑ Cortisol & HPA hyperactivity

↓ BDNF and neuroplasticity

Section 2 — Key Takeaways

1. Brain fog and cognitive fatigue are physiological — driven by measurable disruptions in mitochondrial function, oxidative load, and neurotransmitter balance
2. Oxidative stress creates a self-perpetuating neuroinflammatory cycle that amplifies cognitive symptoms over time
3. Each neurotransmitter has a distinct cognitive role — identifying which system is impaired guides targeted nutraceutical intervention
4. Chronic cortisol elevation is directly neurotoxic, suppressing hippocampal neurogenesis and memory consolidation
5. Sleep disruption impairs glymphatic waste clearance, memory consolidation, and neurotransmitter restoration simultaneously
6. A comprehensive assessment must consider all six drivers — rarely is there a single cause to treat in isolation



Evidence-Based Nutraceuticals

Mechanisms, clinical applications and therapeutic dosing of key cognitive support ingredients

Overview — Five Key Cognitive Nutraceuticals

1. **Creatine Monohydrate**
   Energy & ATP buffer
2. **Magnesium L-Threonate**
   Synaptic plasticity
3. **Nicotinamide Riboside (NR)**
   NAD^+ & mitochondria
4. **L-Theanine**
   Calm alertness & focus
5. **Saffron Extract**
   Mood & neuroprotection
6. **Choline**
   Attention, memory, mental clarity

Selection Criteria

Published RCTs in relevant populations I Defined mechanisms of actions I Established safety profiles I Clinically applicable dosing ranges I Evidence of cognitive or mood outcomes

Evaluation Framework

Level of evidence (RCT, meta-analysis) I Effect size and clinical significance I Population specificity (age, condition) I Bioavailability and form considerations I Interaction ad contraindication profile

Creatine Monohydrate — Brain Energy Reserve

Mechanism of Action

- **Phosphocreatine (PCr) Buffer**
  Creatine is phosphorylated by creatine kinase → stored as PCr; rapidly regenerates ADP→ ATP during high demand
- **Brain Creatine Uptake**
  Brain expresses creatine transporter (SLC6A8); oral supplementation increases cerebral PCr by ~15–20%
- **Neuroprotection**
  Stabilises mitochondrial membrane potential, reduces glutamate excitotoxicity, and attenuates apoptotic cascades
- **Cognitive Energy Buffer**
  Provides rapid ATP resynthesis during cognitively demanding tasks — particularly relevant under stress or sleep deprivation

Clinical Evidence

- ↑ Working memory in vegetarians & sleep-deprived individuals (McMorris et al.)
- ↑ Cognitive processing speed in healthy adults
- ↓ Mental fatigue during sustained cognitive tasks
- Potential benefit in TBI recovery and depression

Dosing & Considerations

- Standard dose: 3–5g/day (monohydrate)
- Timing: with carbohydrate improves uptake
- Form: monohydrate — best evidence, most affordable
- Safety: excellent; may cause mild GI at high doses

Magnesium L-Threonate — Synaptic Density & Memory

Why Magnesium L-Threonate Differs

- **Blood-Brain Barrier Penetration**

  L-Threonate is a vitamin C metabolite that acts as a shuttle, significantly enhancing Mg^{2+} transport across the BBB — unlike oxide or citrate forms

- **NMDA Receptor Modulation**

  Mg^{2+} acts as a voltage-dependent NMDA channel blocker, preventing excitotoxicity while allowing normal LTP induction at optimal concentrations

- **Synaptic Density**

  Magtein™ studies demonstrate increased synaptic density in the prefrontal cortex and hippocampus — key regions for memory and executive function

- **BDNF Upregulation**

  Elevation of brain Mg^{2+} increases BDNF expression, promoting neuroplasticity and new synapse formation

Clinical Evidence

- ↑ Short-term & long-term memory in human RCTs
- ↑ Cognitive performance in older adults (Liu et al.)
- ↓ Sleep-onset latency, ↑ sleep efficiency
- Improved cognitive flexibility and attention

Dosing & Considerations

- Dose: 1,500–2,000mg/day (providing ~144mg elemental Mg)
- Split: 1g morning + 1g evening
- Onset: 6–8 weeks for cognitive benefits
- Form: L-Threonate essential for BBB penetration
- Note: Lower GI side effects than other forms

Nicotinamide Riboside — Restoring NAD^+ Capacity

Mechanism of Action

- **NAD^+ Precursor**

  NR is phosphorylated to NMN by NR kinases (NRK1/2), then adenylated to NAD^+ — bypassing rate-limiting steps of the kynurenine pathway

- **Sirtuin Activation**

  Elevated NAD^+ activates SIRT1, SIRT3 (mitochondrial) — promoting mitochondrial biogenesis via PGC-1α and reducing oxidative stress

- **PARP Substrate**

  PARP enzymes consume NAD^+ for DNA repair; NR supplementation ensures sufficient NAD^+ for both repair and energy metabolism simultaneously

- **Neuronal Protection**

  NR supplementation demonstrates neuroprotection in models of Alzheimer's, Parkinson's and TBI via mitochondrial preservation

Clinical Evidence

- ↑ Blood NAD^+ by 40–50% (Trammell et al. 2016)
- ↑ Muscle mitochondrial function in older adults
- ↓ Markers of neurodegeneration in MCI models
- Improved fatigue scores in clinical trials

Dosing & Considerations

- Dose: 250–500mg/day (standard evidence range)
- Timing: morning (circadian NAD^+ rhythm peaks AM)
- Stability: sensitive to heat and moisture
- Forms: NR chloride (most studied); NMN similar profile
- Note: Flush-free; well tolerated in trials to 2g/day

L-Theanine — Calm Alertness & Cognitive Performance

Mechanism of Action

- **Alpha Wave Induction**

  L-Theanine crosses the BBB and directly increases alpha frequency EEG activity — producing a relaxed-alert state without sedation

- **Glutamate Antagonism**

  Acts as a partial antagonist at NMDA and AMPA receptors, reducing excitatory glutamate transmission and attenuating stress responses

- **GABAergic Enhancement**

  Increases GABA, dopamine and serotonin levels; modulates glycine receptors — contributing to anxiolytic and mood-enhancing effects

- **Synergy with Caffeine**

  L-Theanine counteracts caffeine-induced jitteriness while preserving cognitive enhancing effects — one of the most studied nutraceutical combinations

Clinical Evidence

- ↑ Attention, reaction time & working memory
- ↓ Stress response & cortisol markers
- ↑ Sleep quality (non-sedating at standard doses)
- Theanine + caffeine: consistent cognitive synergy

Dosing & Considerations

- Dose: 200–400mg/day
- For stress/anxiety: 200mg standalone
- With caffeine: 100mg theanine : 50mg caffeine ratio
- Form: L-Theanine (free amino acid form)
- Safety: excellent; no dependency; mild sedation at high doses

Saffron Extract — Mood, Memory & Neuroprotection

Active Constituents & Mechanisms

- **Crocin & Crocetin**

  Carotenoid antioxidants — cross the BBB and exert neuroprotective effects via Nrf2 pathway activation and amyloid-β inhibition

- **Safranal**

  Primary volatile compound — inhibits serotonin, dopamine and noradrenaline reuptake (similar mechanism to SNRIs), improving mood and emotional resilience

- **NMDA Receptor Modulation**

  Crocin modulates NMDA and AMPA receptors, protecting against excitotoxicity and supporting hippocampal LTP and memory formation

- **Anti-inflammatory & Antioxidant**

  Suppresses NF-κB, reduces TNF-α and IL-6, and prevents lipid peroxidation — directly addressing neuroinflammatory drivers of cognitive decline

Clinical Evidence

- Non-inferior to fluoxetine in mild-moderate depression RCTs
- ↑ Memory and learning in MCI (Akhondzadeh et al.)
- ↓ Anxiety symptoms; ↑ sleep quality
- Potential benefit in menopausal mood symptoms

Dosing & Considerations

- Dose: 28–88mg/day (standardised extract)
- Most studied: 30mg Affron® or Saffr'Activ®
- Onset: 4–8 weeks for mood effects
- Caution: uterotonic in high doses (pregnancy)
- Interaction: potential serotonergic synergy — monitor with SSRIs

Choline — Cognitive Architecture, BDNF & Hormonal Brain Health

Choline is an essential nutrient for brain structure, neurotransmission, epigenetic regulation and neuroplasticity — chronically under-consumed

- **Acetylcholine Synthesis**
  Choline + acetyl-CoA → acetylcholine via choline acetyltransferase (ChAT) — primary neurotransmitter for memory encoding, attention and executive function
- **Phosphatidylcholine & Membrane Integrity**
  Essential component of phosphatidylcholine (PC), the dominant neuronal membrane phospholipid — critical for synaptic plasticity, signal transduction and repair
- **BDNF Upregulation**
  Choline supplementation upregulates BDNF expression and its receptor TrkB, promoting neuroplasticity, hippocampal neurogenesis and long-term memory consolidation
- **Methylation & Epigenetics**
  Choline is a methyl donor via the one-carbon pathway (choline → betaine → homocysteine remethylation), supporting DNA methylation and gene expression in ageing
- **Brain Fog & Cognitive Performance**
  Low ACh → impaired attention, word retrieval, mental slowness. CDP-choline & Alpha-GPC show ↑ memory and attention in RCTs
- **BDNF & Neuroplasticity**
  Choline deficiency reduces hippocampal BDNF, impairing learning and adaptive cognition. Synergistic with exercise-induced BDNF elevation
- **Post-Menopausal Brain Health**
  Oestrogen upregulates choline biosynthesis via PEMT pathway — post-menopause this is impaired, increasing requirements to 550mg+/day. Deficiency linked to ↑ cognitive decline
- **Men's Brain Health**
  Men have higher baseline requirements (550mg/day AI) and higher deficiency rates. Low choline linked to accelerated age-related cognitive decline. CDP-choline benefits attention and processing speed

Forms & Dosing: CDP-Choline (Citicoline): 250–500mg/day | Alpha-GPC: 300–600mg/day | Phosphatidylcholine: 1–3g/day | Choline Bitartrate: 500–1,000mg/day | Food sources: eggs, liver, salmon, soy

Comparative Overview — Nutraceutical Targets

Ingredient	Primary Target	Key outcome	Dose Range	Evidence Level
Creatine	Brain energy (PCr buffer)	Working memory, mental fatigue	3-5g/day	★★★★☆ Multiple RCTs
Mg L-Threonate	Synaptic density (NMDA/BDNF)	Memory, sleep, cognitive flexibility	1.5-2g/day	★★★★☆ Human & animal RCTs
NR (Nicotinamide Riboside)	NAD^+ restoration (mitochondria)	Fatigue, cellular energy, neuroprotection	250–500mg/day	★★★☆☆ Emerging RCTs
L-Theanine	Alpha waves, glutamate/GABA	Calm focus, stress, sleep	200–400mg/day	★★★★☆ Multiple RCTs
Saffron Extract	Serotonin/DA reuptake, antioxidant	Mood, memory, anxiety	28–88mg/day	★★★★☆ Multiple RCTs
Choline	Acetylcholine synthesis, phospholipid/membrane support	Attention, memory, mental clarity	550-1100mg/day	★★★☆☆ Emerging human RCTs

Section 3— Key Takeaways

1. Creatine monohydrate provides a rapid phosphocreatine buffer — supporting ATP resynthesis in neurons during high-demand cognitive tasks
2. Magnesium L-Threonate is the only magnesium form with established BBB penetration, increasing synaptic density and BDNF in the hippocampus
3. Nicotinamide riboside restores declining NAD^+ levels, activating sirtuins and mitochondrial biogenesis pathways
4. L-Theanine produces a uniquely calm-alert state via alpha wave induction, with synergistic benefit when combined with caffeine
5. Saffron extract (30mg standardised) demonstrates efficacy comparable to low-dose antidepressants in mood and memory outcomes
6. All six nutraceuticals have published RCT data — ingredient form, standardisation and dose are critical determinants of efficacy

Case Study

What this can look like in practice

Liz – 57yr old GP / Neuroscientist

- APOE E4/E3 – her mum has vascular dementia, white matter issues, severe mental health problems
- Mould Illness / CIRS – 2012-2013 after moving into new apartment – after remediation, relocated
- Cognition DEF worse for severe stress and/or alcohol consumption

- Numerous head injuries
- Many antibiotics, esp in 6mth prior to initial consultation
- HRT – 2yrs
- IF & ketosis – 12mths prior
- Retired 6mths into treatment

Now – 1yr into treatment / BrainScan, CNS Vital Signs both normal, Lumosity >95% of age group

Liz's Story

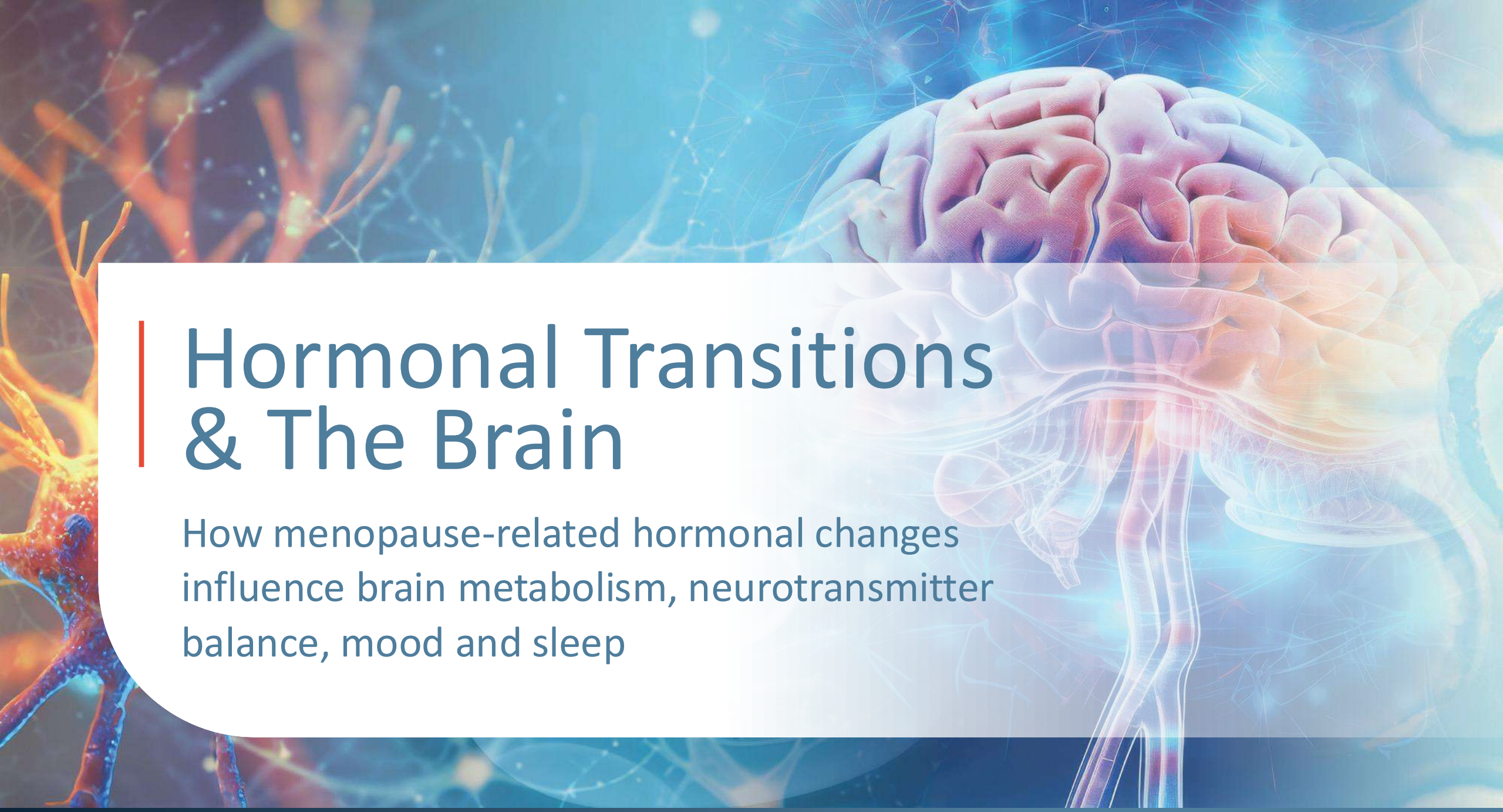
"I have been consulting with Jo regarding cognitive health for over 12 months. Under her care and guidance, I have made some incredible gains which are reflected in my test results, my cognitive scores and more importantly the ease with which I can now enjoy and move through my everyday life!

Despite having some prior knowledge regarding cognitive health, I could not achieve this level of improvement until I found the advice, support, encouragement and specific skills and suggestions that Jo brings to her work.

It is a pleasure to work with Jo who brings a kindness and professionalism to her approach. I would highly recommend Jo to anyone concerned about improving or retaining their cognitive health."

Liz J

Aged 58



Hormonal Transitions & The Brain

How menopause-related hormonal changes influence brain metabolism, neurotransmitter balance, mood and sleep

Oestrogen as a Neuroprotective Hormone

Oestrogen is not merely a reproductive hormone — it is a potent neuroactive steroid with widespread effects on brain metabolism and function

- **Mitochondrial function**
  Oestrogen (E2) stimulates mitochondrial biogenesis via ERα and ERβ receptors; maintains oxidative phosphorylation efficiency in neurons
- **Neurotransmitter Regulation**
  Modulates serotonin, dopamine and acetylcholine synthesis and receptor sensitivity; maintains monoamine oxidase inhibition
- **Neuroprotection**
  Anti-inflammatory, antioxidant and anti-apoptotic properties; suppresses NF-κB and amyloid precursor protein processing
- **Glucose Metabolism**
  E2 upregulates GLUT1 and GLUT3 transporters in the BBB and neurons, maintaining cerebral glucose uptake — drops sharply at menopause
- **Synaptic Plasticity**
  Promotes dendritic spine density in the hippocampus and prefrontal cortex; upregulates BDNF; supports LTP and memory consolidation
- **Circadian & Sleep Regulation**
  Modulates melatonin secretion and sleep architecture; declining E2 disrupts sleep onset, depth and continuity

The Menopausal Transition — A Neurological Event

Perimenopause and menopause trigger measurable changes in brain energy metabolism, neurochemistry and structure

1

Perimenopause (~45-51)

Fluctuating oestrogen; early cognitive changes; increased mood variability; sleep disruption begins

2

Menopause (~51 avg onset)

Sustained oestrogen decline; peak cognitive symptoms; hot flushes disrupt sleep; brain glucose metabolism ↓

3

Post-menopause (Years 1-5)

Adaptation phase; some neurological compensation; window of therapeutic opportunity; cognitive risk stratification important

4

Long –term Post-menopause

Elevated Alzheimer's risk in genetically predisposed; ongoing impact of sleep quality and metabolic syndrome on cognition

Oestrogen, Serotonin & Mood Dysregulation

Oestrogen-Serotonin Axis

- E2 upregulates tryptophan hydroxylase (TPH) — the rate-limiting enzyme in serotonin synthesis
- E2 downregulates MAO-A, reducing serotonin degradation
- E2 increases 5-HT_2A receptor sensitivity in the prefrontal cortex
- Declining E2 = reduced serotonergic tone → mood instability, irritability, low mood

Dopamine & Motivation

- E2 stimulates dopamine release in the mesolimbic system
- Progesterone fluctuations alter dopamine receptor sensitivity
- Declining hormones → reduced reward processing → anhedonia and apathy

Menopausal Mood Symptom Profile

Low mood/depression	38%
Anxiety/Irritability	44%
Emotional lability	52%
Cognitive fog	60%
Sleep disruption	61%
Reduced resilience	47%

Sleep Architecture Changes in Menopause

Sleep disruption in menopause is multifactorial — a convergence of hormonal, thermoregulatory and neurotransmitter changes

- **Vasomotor Symptoms (Hot Flushes/Night Sweats)**
  Hypothalamic thermoregulatory dysfunction from declining E2 triggers nocturnal awakenings; disrupts deep sleep and REM consolidation
- **Progesterone Decline**
  Progesterone has GABAergic and hypnotic properties via allopregnanolone; loss increases sleep-onset latency and reduces slow-wave sleep
- **Serotonin Disruption**
  Serotonin is a melatonin precursor; declining serotonin delays melatonin onset and reduces sleep pressure, causing fragmented patterns
- **Cortisol Dysregulation**
  HPA axis dysregulation elevates nocturnal cortisol, preventing restorative deep sleep and increasing early morning awakening
- **Sleep Apnoea Risk**
  Post-menopausal women have significantly higher rates of obstructive sleep apnoea — a frequently overlooked driver of cognitive impairment

Brain Metabolism & the Energetic Crisis of Menopause

Neuroimaging reveals a metabolic shift in the menopausal brain — with significant implications for long-term cognitive health

- **Glucose Hypometabolism**

  FDG-PET studies show 15–20% reduction in cerebral glucose uptake in parietal, temporal and frontal regions during perimenopause
  (Mosconi et al., 2017–2021)

- **Ketone Compensation**

  As glucose metabolism declines, the menopausal brain begins utilising ketones — a potential therapeutic window for ketogenic diet or MCT supplementation

- **White Matter Changes**

  Longitudinal MRI studies document white matter hyperintensities emerging during hormonal transition — correlating with vasomotor symptom severity

- **Mitochondrial Remodelling**

  E2 receptor signalling directly regulates Complex I and IV activity; oestrogen withdrawal reduces mitochondrial efficiency and increases ROS production

- **Amyloid-β Accumulation**

  Reduced glucose metabolism is associated with increased amyloid-β deposition — **perimenopause may represent a critical window for Alzheimer's risk modification**

- **Neuroinflammation**

  Declining E2 removes its anti-inflammatory CNS protection — microglial activation increases, contributing to the chronic neuroinflammatory burden

Nutraceutical Opportunities in Hormonal Transition

Targeting the specific neurological changes of menopause with evidence-based nutraceuticals

Brain Energy Decline	Creatine + NR	Support PCr buffering and NAD^+-dependent mitochondrial function to compensate for declining oestrogen-driven metabolism
Mood & Serotonin	Saffron 30mg/day	Monoamine reuptake inhibition and 5-HT receptor modulation directly addresses oestrogen-withdrawal serotonin deficit
Sleep Quality	Mg L-Threonate + L-Theanine	Mg^{2+} supports GABAergic calm; L-Theanine promotes alpha wave relaxation — both address sleep-onset and quality disruption
Cognitive Fog	Mg L-Threonate + Saffron + Creatine	Combination approach addressing synaptic density, neuroprotection, and energy buffering — targets multiple mechanisms of menopausal brain fog
Oxidative Stress	NR + Saffron extract	NR supports mitochondrial antioxidant defence; saffron crocins directly scavenge ROS and activate Nrf2 pathway

Section 4— Key Takeaways

1. Oestrogen is a powerful neuroprotective hormone — its decline at menopause triggers measurable changes in brain metabolism, neurotransmitter balance and structure
2. PET imaging confirms reduced cerebral glucose metabolism during perimenopause, beginning before the final menstrual period
3. Serotonin deficit from declining oestrogen directly underlies mood instability, irritability and low mood in the menopausal transition
4. Sleep disruption in menopause is multifactorial — vasomotor symptoms, progesterone loss, cortisol elevation and serotonin decline all contribute
5. The menopausal brain faces an 'energetic crisis' — creating specific targets for mitochondrial, NAD^+, and synaptic support nutraceuticals
6. Perimenopause may represent a critical therapeutic window — early intervention can modulate long-term cognitive and Alzheimer's risk trajectories

BDNF

Patient handout available after presentation

BDNF helps the brain learn, adapt and recover

Brain-derived neurotrophic factor acts like “fertilizer” for the brain- supporting new connections, memory, mood and resilience.

- **Learning and Memory**

Helps the brain build and strengthen connection

- **Mood & Resilience**

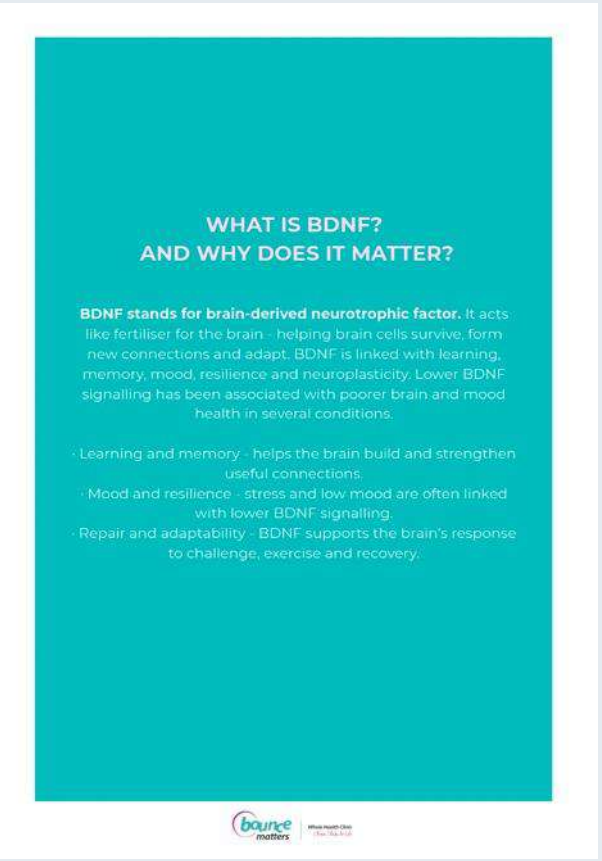
Stress and low mood are often linked to lower BDNF signalling

- **Repair and Adaptability**

Supports the brain’s response to challenge, exercise and recovery.

What matters most in practice

Everyday BDNF support is shaped by how we sleep, move, eat, manage stress and challenge the brain- making it a useful closing lens for brain energy, mood and cognitive resilience.



From the BDNF patient handout

A patient-friendly take-home summary will be provided after the presentation

How to support BDNF after today

The handout emphasises foundations first: movement, sleep daylight, stress regulation, brain challenge and a colourful fibre-rich diet – with supplements as an adjunct.

1. Move most days

Prioritise aerobic activity, plus some resistance training across the week.

2. Protect sleep + daylight

Keep a regular sleep window and aim for morning/daytime light exposure.

3. Lower chronic stress

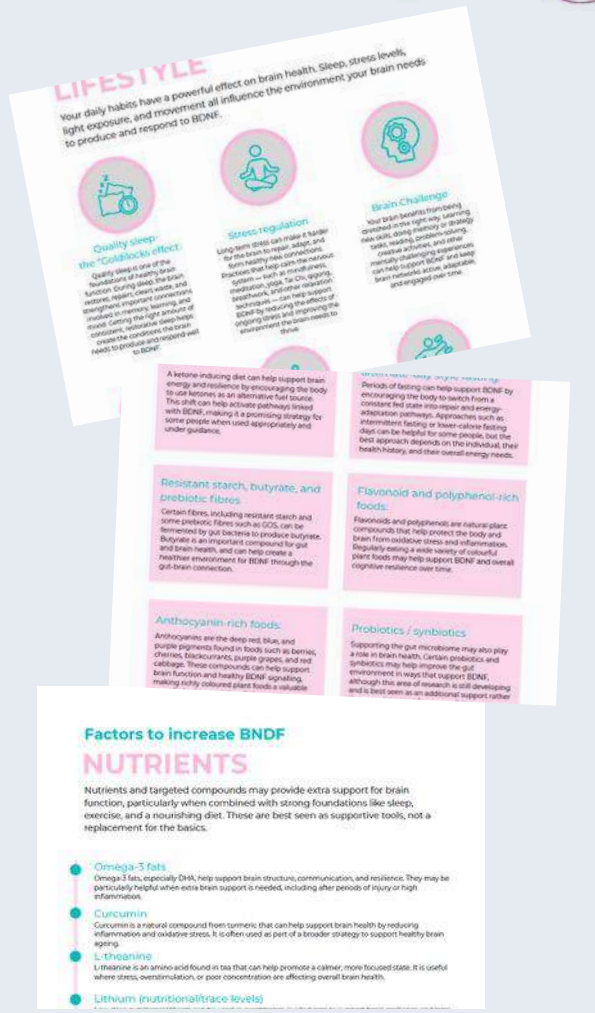
Use calming practices and keep the brain engaged with learning and challenge.

4. Build brain-supportive meals

Think colourful plants, extra fibre, regular protein, berries, herbs/spices and olive oil.

5. Use targeted support wisely

Explore supplements options – alongside the basics and with guidance where needed.



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Layered Clinical Strategy

Developing a personalised nutraceutical approach that supports brain energy,cognitive performance, stress resilience and emotional wellbeing

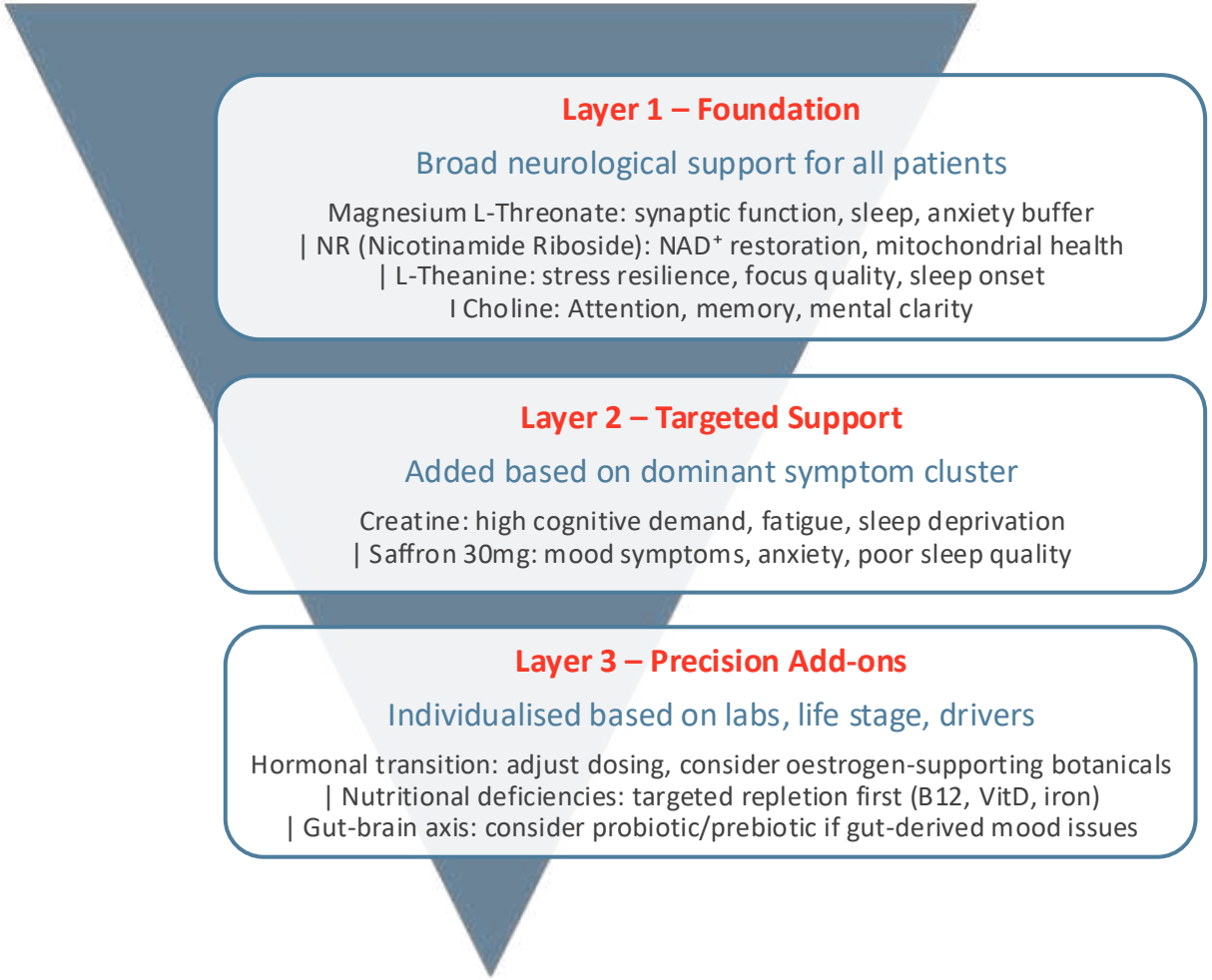
Clinical Assessment Framework

A personalised nutraceutical strategy begins with identifying which physiological systems are most impaired*

- **Energy & Mitochondria**
  Persistent fatigue unrelieved by rest?
  Post-exertional malaise? History of viral illness?
- **Cognition & Memory**
  Brain fog- when does it occur?
  Working memory, word retrieval, processing speed?
- **Stress & HPA Axis**
  Chronic life stressors or trauma history?
  Cortisol timing- wired at night? Burnout?
- **Mood & Neurotransmitters**
  Low mood, anhedonia, anxiety, irritability?
  Hormonal pattern (cycle, perimenopausal, HRT)?
- **Sleep Architecture**
  Sleep onset vs maintenance insomnia?
  Night sweats, temperature dysregulation, apnoea?
- **Nutrient & Hormonal Status**
  Labs: B12, folate, ferritin, VitD, thyroid, homocysteine, etc?
  Sex hormones (Oestadiol, progesterone, DHEA)?

The Layered Nutraceutical Model

A three-layer framework: Foundation → Targeted Support → Precision Personalisation



Clinical Scenarios — Tailoring the Protocol

- **High-Achieving Professional, Stress Driven Brain Fog**

  Patient Profile: *High workload, poor sleep, afternoon cognitive crash, anxiety, reliant on caffeine*

  Suggested Protocol: L-Theanine 200mg + caffeine AM / Mg L-Threonate 1g AM + 1g PM / NR 250mg AM / Consider: creatine 3g daily

- **Perimenopausal Woman, Mood & Sleep Disruption**

  Patient Profile: *Irregular cycles, poor sleep, low mood, hot flushes, brain fog, anxiety episodes*

  Suggested Protocol: Saffron 30mg AM / Mg L-Threonate 2g PM / L-Theanine 200mg PM / NR 250mg AM / Consider: creatine for energy

- **Post-Menopausal, Memory & Focus Concerns**

  Patient Profile: *HRT consideration pending, word retrieval difficulty, low energy, mild depression*

  Suggested Protocol: NR 500mg AM / Creatine 3–5g daily / Mg L-Threonate 2g PM / Saffron 30mg AM / Reassess at 8 weeks

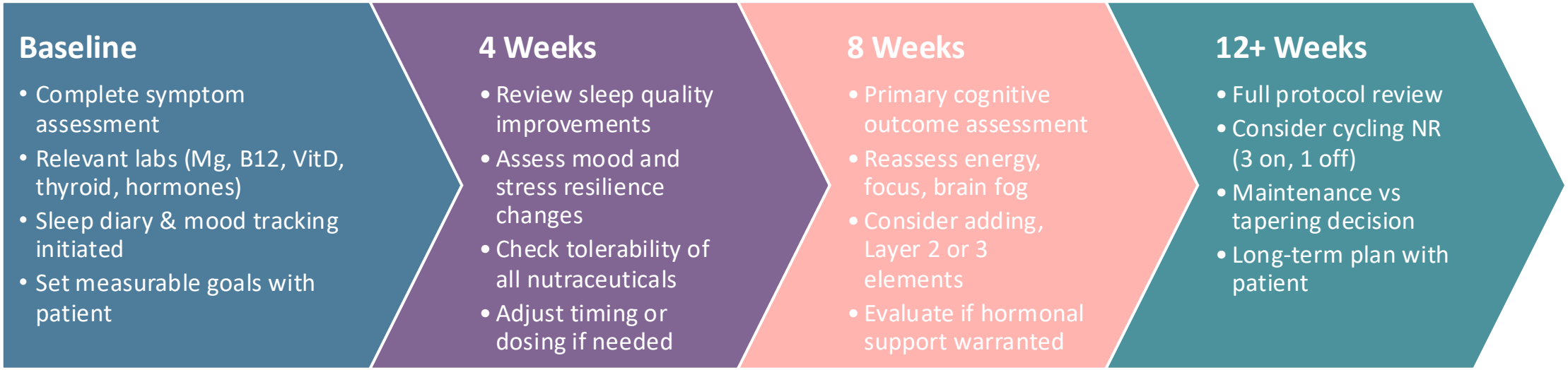
- **Chronic Fatigue Pattern, Post-viral Cognitive Impairment**

  Patient Profile: *Post-infection fatigue, brain fog, poor exercise tolerance, disrupted sleep*

  Suggested Protocol: NR 500mg AM / Creatine 3g daily / Mg L-Threonate 1g AM + 1g PM / L-Theanine 200mg / Avoid stimulants initially

Monitoring, Review & Optimisation

Effective clinical application requires structured monitoring and a clear review timeline



Drug-Nutrient Interactions & Contraindications

Nutraceutical	Interaction	Risk	Clinical Guidance
Saffron Extract	SSRIs/SNRIs	Moderate	Additive serotonergic effect; potential serotonin syndrome at high doses — monitor carefully, start low, avoid high-dose combinations
NR (Nicotinamide Riboside)	Chemotherapy agents	Moderate	Theoretical concern: NR may upregulate NAD^+ in cancer cells; discuss with oncologist before use in active cancer treatment
Magnesium	Bisphosphonates, Fluoroquinolones	Low-Mod	Magnesium chelates these medications, reducing absorption — separate dosing by 2+ hours
Creatine	NSAIDs, diuretics, nephrotoxic agents	Low	Theoretical renal load concern with existing kidney impairment; not recommended in moderate-severe CKD — check eGFR
L-Theanine	Antihypertensives, sedatives	Low	Additive blood pressure lowering; mild additive sedation with benzodiazepines — monitor in sensitive patients

Sample Daily Protocol — Perimenopausal Cognitive Support

An illustrative evidence-based protocol for a perimenopausal patient with mood, sleep and cognitive symptoms

Morning (with breakfast)	NR 250mg	NAD^+ restoration — aligned with circadian peak
	Creatine 3g	Brain energy buffer — early cognitive demands
	Safron 30mg	Mood & serotonin support — early day mood set
	L-Theanine 100mg	If caffeinated: counteract jitteriness
Evening (with dinner)	Mg L-Threonate 1g	Synaptic Support — first dose
Bedtime (30-60 min before bed)	Mg L-Threonate 1g	Second dose — sleep onset and quality support
	L-Theanine 200mg	Alpha wave induction — relaxation without sedation
	Creatine 5g	

Section 5— Key Takeaways

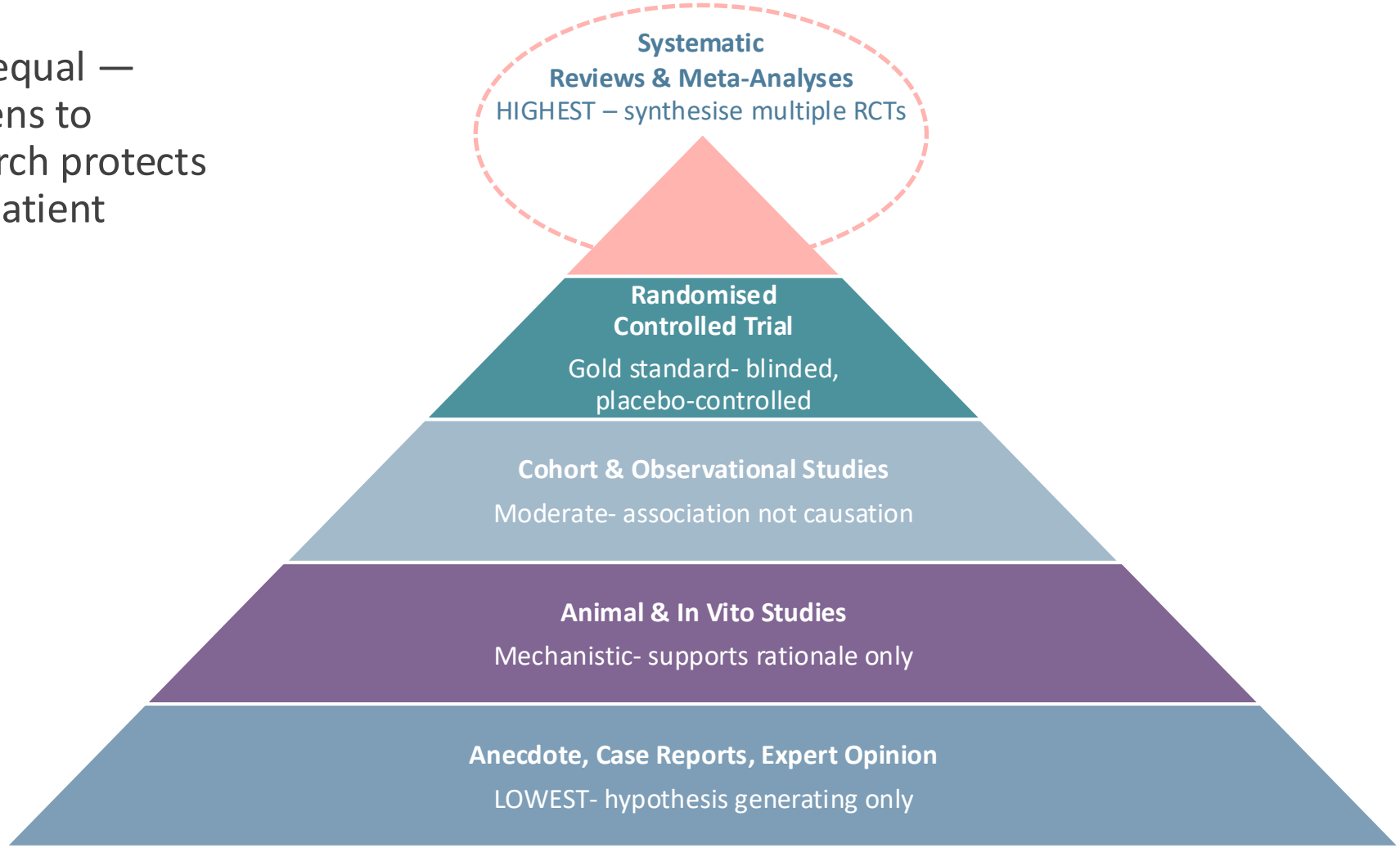
1. A layered clinical strategy — Foundation → Targeted → Precision — allows systematic, evidence-based protocol construction
2. Clinical assessment must address all six symptom domains: energy, mood, cognition, sleep, stress, and nutritional/hormonal status
3. Protocols should be tailored to life stage, dominant symptom cluster, medications, and patient-specific goals
4. Saffron requires caution with concurrent serotonergic medications; all interactions should be screened at prescription
5. A structured review at 4, 8 and 12 weeks with validated outcome tools enables evidence-informed optimisation
6. The most effective protocols combine synergistic mechanisms — addressing energy, neuroprotection, mood and sleep simultaneously

Critically Assessing Nutraceutical Quality

Evaluating ingredient standardisation, bioavailability, evidence quality and clinically relevant dosing to support evidence-based prescribing

Evidence Quality — Reading the Research

Not all evidence is equal — applying a critical lens to nutraceutical research protects both clinician and patient



Ingredient Standardisation — Why It Matters

Standardisation guarantees a defined minimum of active constituents — without it, clinical outcomes cannot be replicated

Ingredient	Branded Form	Standardisation	Clinical Rationale
Saffron Extract	Affron® / Saffr'Activ®	≥3.5% Lepticrosalide (crocin + safranal profile)	Generic saffron has highly variable crocetin and safranal content — studies use standardised brands; generic ≠ clinical dose
NR (Nicotinamide Riboside)	Tru Niagen® / Niagen®	NR chloride salt (not NR free base)	NR chloride is the form used in pharmacokinetic studies confirming NAD^+ elevation — other forms lack equivalent data
Magnesium L-Threonate	Magtein™	L-Threonate chelate (not other Mg forms)	Only Mg L-Threonate (Magtein™) has demonstrated BBB penetration and hippocampal Mg elevation in RCTs
Bacopa (reference)	BacoMind® / KeenMind®	≥55% Bacosides A+B	Non-standardised bacopa can contain <10% bacosides — inadequate to replicate clinical memory outcomes

Ingredient Standardisation — Why It Matters

The most evidence-rich ingredient is ineffective if it cannot be absorbed and delivered to the target tissue

Ingredient	Best Form(s)	Avoid/Weaker	Key Bioavailability Factor
Magnesium	L-Threonate (brain) Glycinate (systemic)	Oxide (~4% absorption)	L-Threonate: unique BBB penetration via active transport — essential for cognitive indication
Creatine	Monohydrate (micronised)	Creatine HCl (no RCT advantage)	Monohydrate has the most evidence and best cost-efficacy; take with carbohydrate for enhanced uptake
Saffron (Crocins)	Standardised extract (Affron®, 28–88mg)	Culinary saffron (variable, not dosed)	Bioavailability enhanced by lipophilic matrix; enteric coating protects active constituents
NR	NR chloride (room temp stable)	Heat-degraded or improperly stored NR	NR is pH and heat sensitive; packaging quality and cold chain matter for potency retention
L-Theanine	Free amino acid form (Suntheanine® or eq.)	Green tea extracts (variable, lower dose)	Rapidly absorbed; peak plasma at 50 min; crosses BBB via neutral amino acid transporter

Clinically Relevant Dosing — What the Evidence Shows

1 Brain 1 Body for Life

Therapeutic dosing is defined by what was used in successful clinical trials — not manufacturer minimums

Nutraceutical	Effective Dose	Insufficient Dose	Clinical Rationale
Creatine	3–5g/day (maintenance)	<1g/day (typical in blends)	Studies showing cognitive benefit used ≥3g/day standalone; proprietary blends often provide 200–500mg — sub-therapeutic
Mg L-Threonate	1,500–2,000mg/day (Magtein™)	<1,000mg/day	Animal studies showing hippocampal benefit required raising brain Mg^{2+} by ~15% — requires 1.5–2g daily dose
NR	250–500mg/day	<150mg/day	NAD^+ elevation studies used 250mg minimum; 500mg shows faster, more robust elevation in clinical pharmacokinetics
L-Theanine	100–400mg/day (goal-dependent)	<50mg/day	Alpha wave studies used 50–200mg; sleep benefit requires 200mg; sub-50mg doses produce minimal EEG changes
Saffron	28–88mg/day (standardised)	Unstandardised, <15mg/day	RCTs consistently used 28–30mg of standardised extract; mood outcomes not replicated at lower or generic doses

Manufacturing Quality — What to Look For

- **GMP Certification (ESSENTIAL)**
  Good Manufacturing Practice (TGA GMP for AU; NSF, USP for US/EU) confirms standardised manufacturing, testing and quality control processes
- **Third-party Testing (ESSENTIAL)**
  Independent verification of identity, potency and purity (heavy metals, pesticides, microbiological contaminants) — more reliable than manufacturer testing alone
- **Certificate of Analysis (CoA) (ESSENTIAL)**
  Document confirming batch-specific testing of active ingredient potency — should be available for every product lot on request
- **Branded Ingredient Use (PREFERRED)**
  Utilisation of patented, clinically studied forms (Magtein™, Affron®, Tru Niagen®) — guarantees the form used in clinical research
- **Transparent Labelling (PREFFERED)**
  Full ingredient disclosure including form, standardisation, dose per serving —no 'proprietary blends' masking individual doses
- **Additive & Filler Profile (CONSIDER)**
  Minimal excipients; no titanium dioxide, artificial colours; consideration of allergen status (gluten, dairy, soy); capsule material (vegetarian/vegan)

Evidence-Based Prescribing Checklist

A practical checklist for every nutraceutical recommendation — ensuring clinically defensible practice

Evidence:	Form & Standard:	Dosing:	Quality:	Safety:
RCT in a comparable patient population?	Same ingredients form as used in trials?	Product dose matches effective trial dose?	GMP-certified by recognised body?	Drug-nutrient interactions screened?
Clinically meaningful effect size?	Standardisation active constitute percentage?	Not hidden in a proprietary blend?	Third-party testing and CoA available?	Contradictions for this specific patient?
Independent replication- noy only industry-funded?	Branded form with published bioavailability?	Dose frequency matches pharmacokinetics?	Excipients and allergens clearly disclosed?	Safety database exists for dose range?

Section 6 – Key Takeaways

1. Not all evidence is equal — RCTs in comparable populations with clinically relevant doses and independent replication are the gold standard
2. Ingredient form is critical: Mg L-Threonate ≠ Mg oxide; NR chloride ≠ generic niacinamide — always specify the form used in research
3. Standardisation ensures reproducibility — without a defined active constituent percentage, therapeutic outcomes cannot be reliably achieved
4. Therapeutic dosing is defined by the evidence: most cognitive nutraceuticals are significantly under-dosed in combination products
5. GMP certification, third-party testing, and accessible CoAs are the minimum quality standards for responsible clinical recommendation
6. Evidence-based prescribing requires a systematic checklist approach — combining evidence, form, dose, quality and safety screening

The brain doesn’t fail suddenly—it struggles first!

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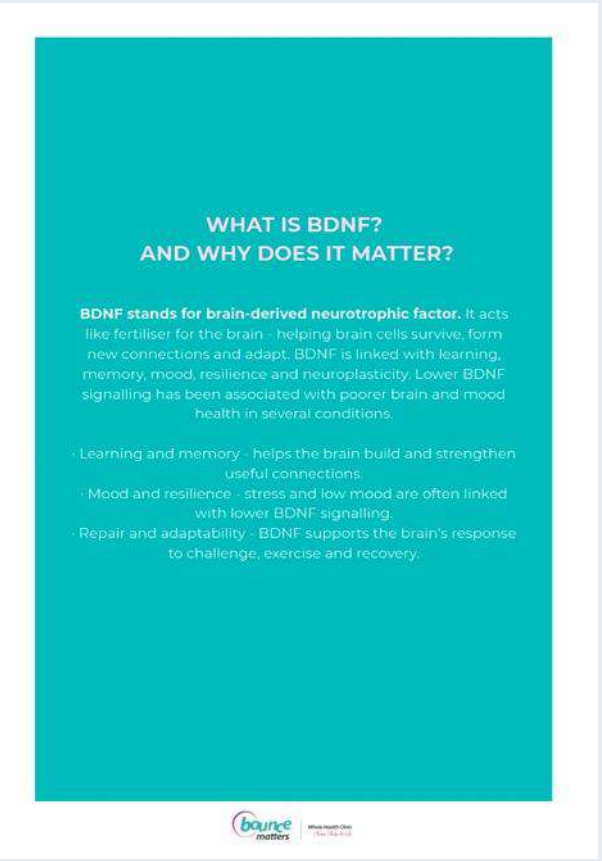

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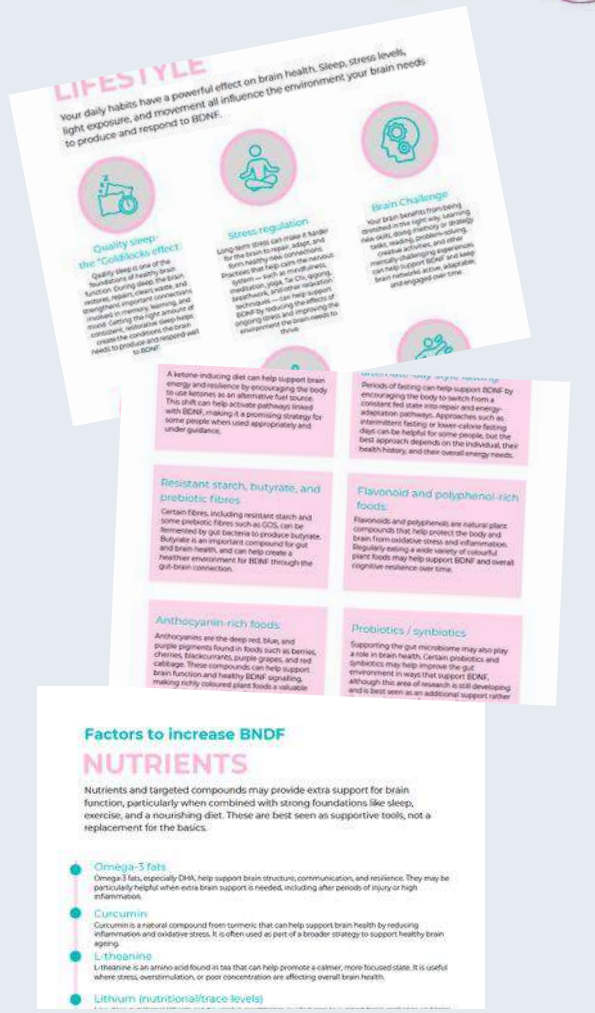

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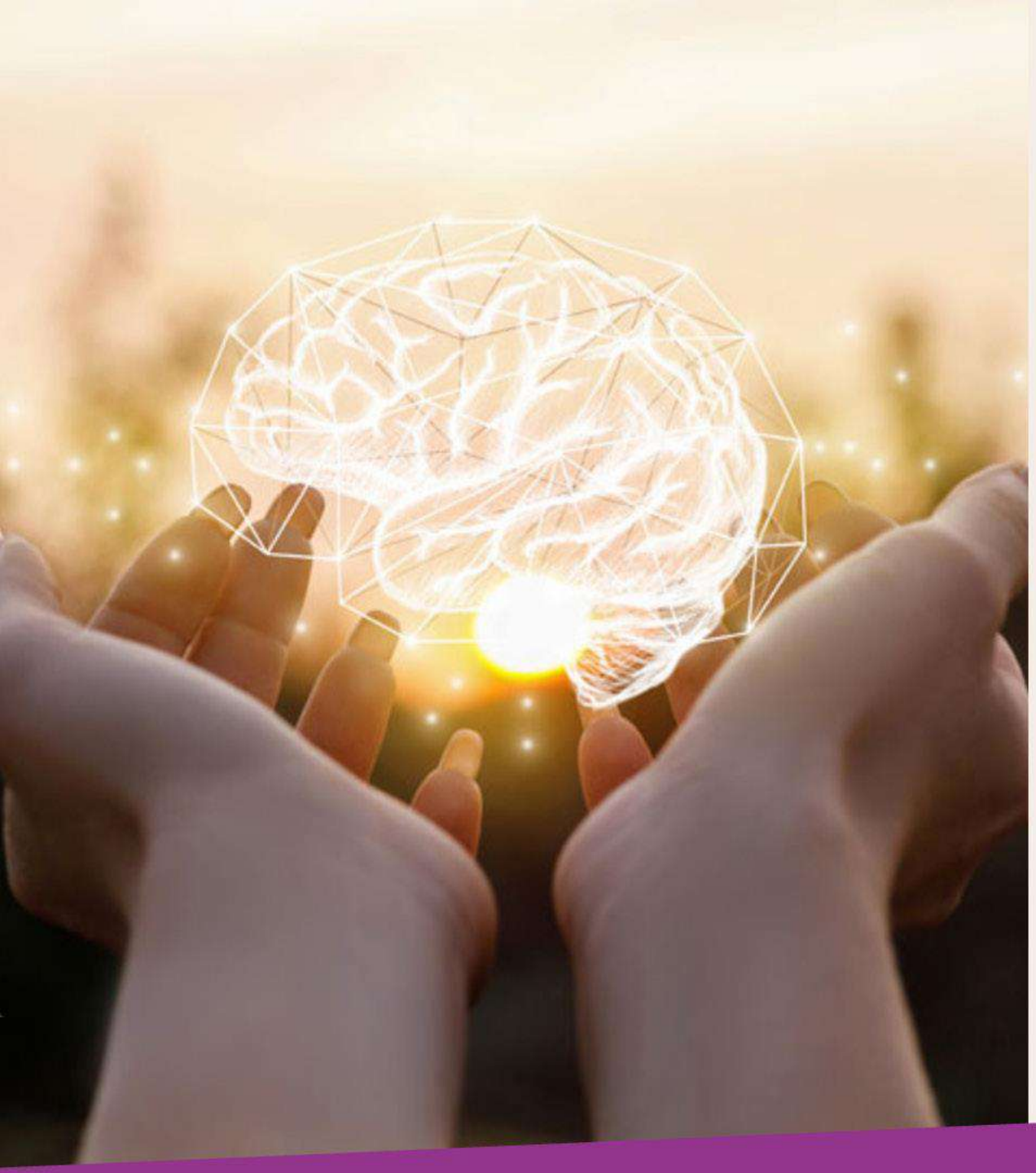
FREE 90-minute Masterclass

What you'll learn:

- The root causes of cognitive decline most practitioners miss
- Which labs and tests matter most (and how to use them)
- Nutrition and lifestyle interventions that improve brain resilience
- How to translate cutting-edge research into your clinic.



Connect with me!
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Thank you & we really hope to see you next week!

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