How to improve memory

A review of nootropics & other options for MCI and TBI

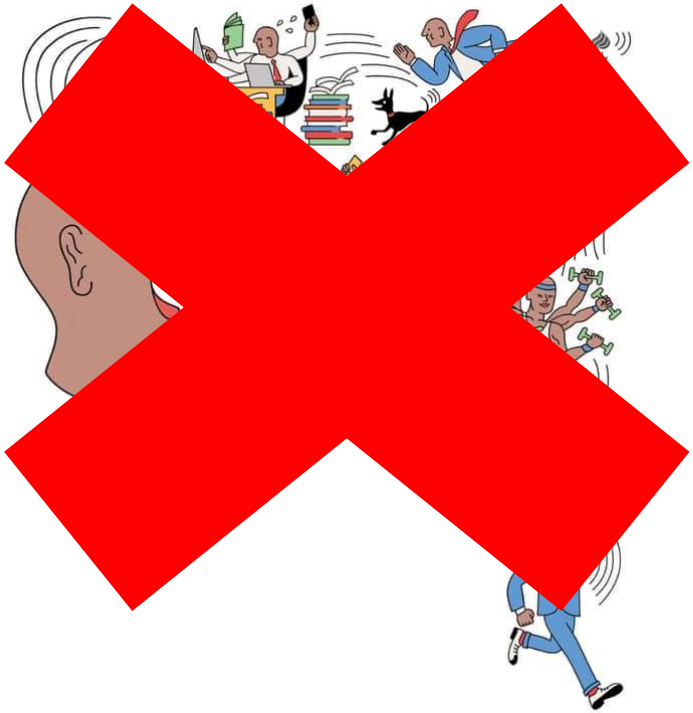
integrative mental health CONFERENCE 23

Tim Ewer

MB ChB, MMedSc, MRCP, FRACP, FRNZCGP, FACNEM, Dip Occ Med, DCH, DRCOG

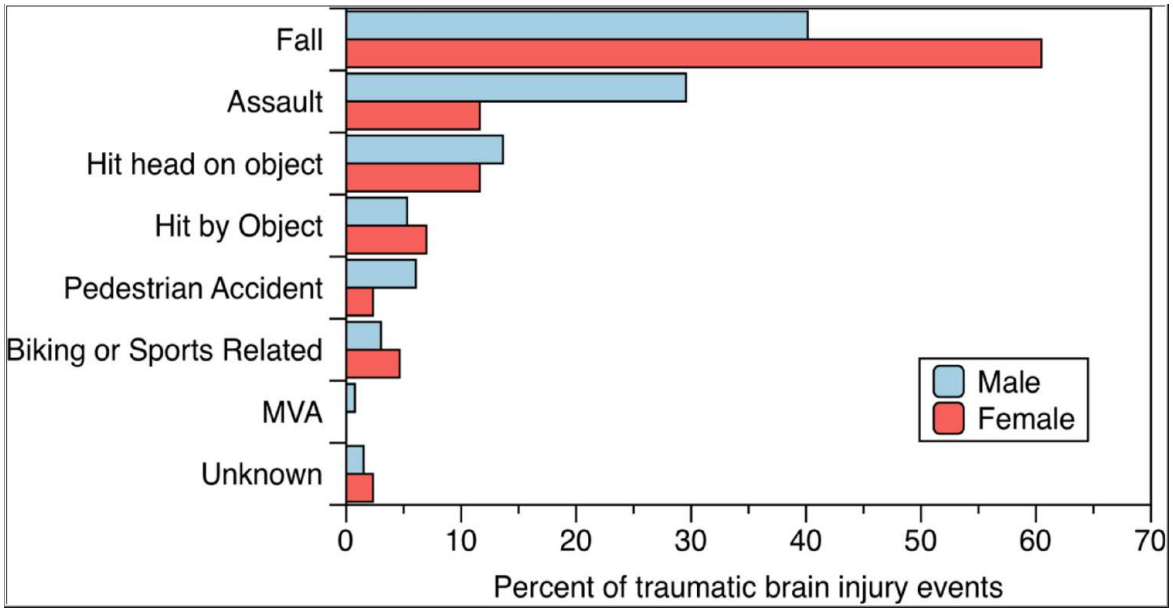
Objectives

- Defining the problem
- Basic nutrients
- Nootropics
  - Nutritional
  - Herbal
  - Medical
- Lasers
- HBOT
- Neural training + Neurofeedback



Traumatic brain injury - TBI

- nondegenerative, noncongenital insult to the brain from an external mechanical force
- possibly leading to permanent or temporary impairment of cognitive, physical, and psychosocial functions, with an associated diminished or altered state of consciousness



EClinicalMedicine. 2022 Feb 1;44:101277

Severity of TBI

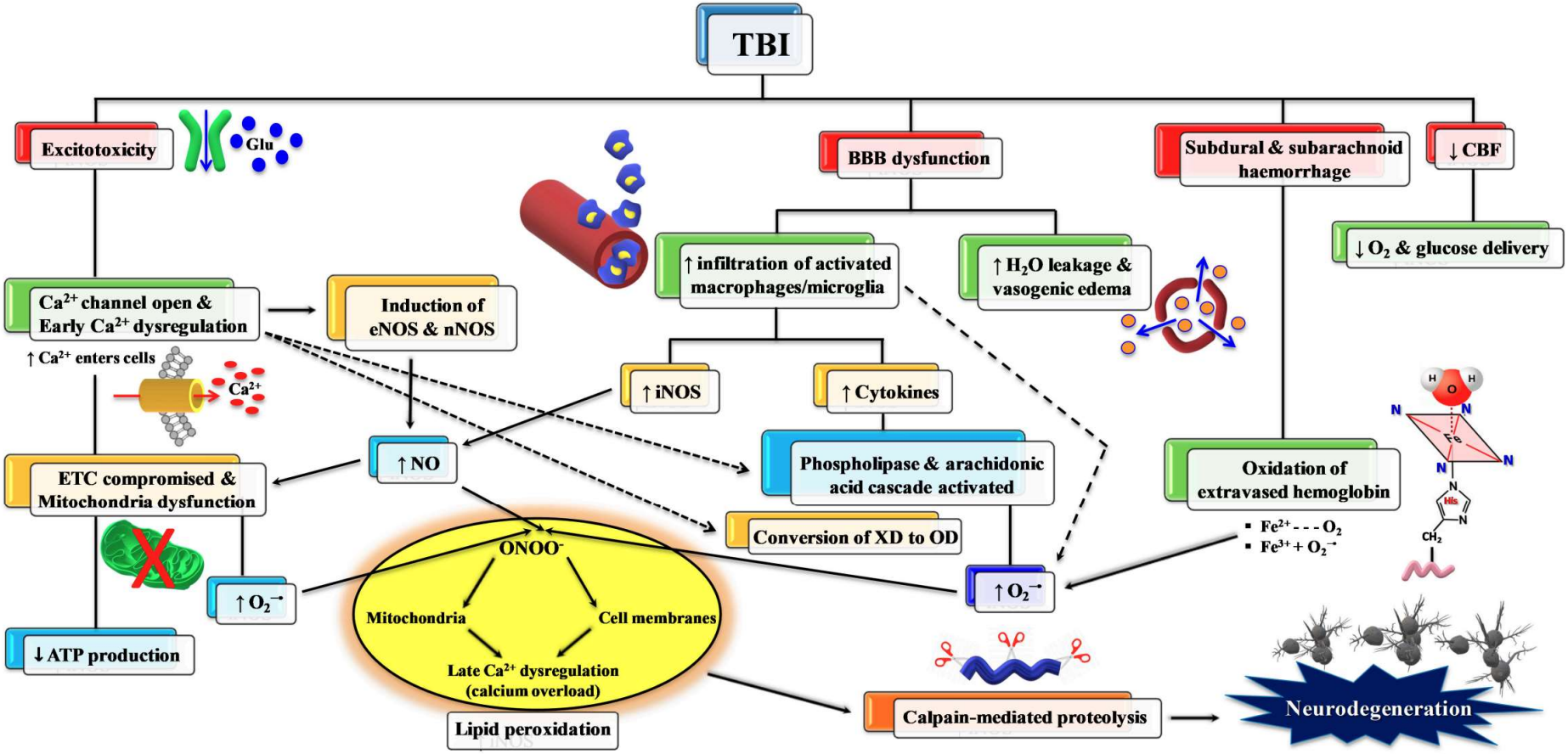
- According to GCS score (in first 48 hours)
  - Severe TBI = 3-8
  - Moderate TBI = 9-12
  - Mild TBI = 13-15
- In the UK, annually there are 900,000 A&E attendances
- 1.3 million living with disabilities from TBI
- Vast majority of head injuries are not seen
- Costs of TBI in K is estimated at £15 billion (0.8% of GDP) per year

Medical Research Council Report on TBI. June 2022

Behaviour	Response
 Eye Opening Response	4. Spontaneously 3. To speech 2. To pain 1. No response
 Verbal Response	5. Oriented to time, person and place 4. Confused, but able to answer Qs 3. Inappropriate words 2. Incomprehensible sounds 1. No response
 Motor Response	6. Obeys commands 5. Moves to localised pain 4. Flex to withdraw from pain 3. Abnormal flexion, decorticate posture 2. Abnormal extension, decerebrate posture 1. No response

Glasgow Coma Scale (GCS)

TBI main pathophysiology

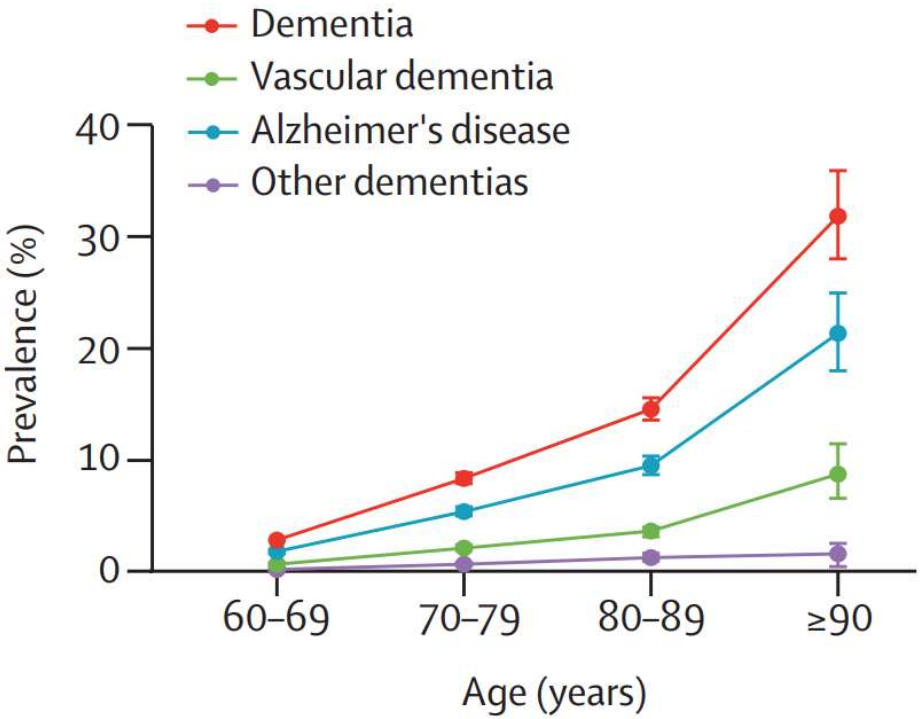


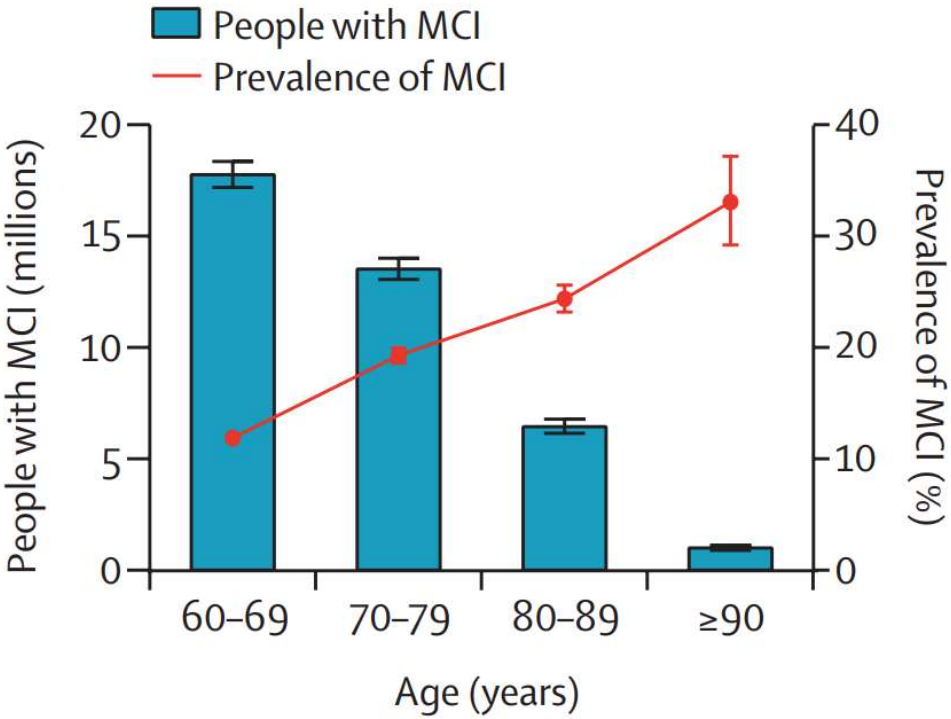
Antioxidants 2020, *9*(3), 260;

MCI - mild cognitive impairment

- MCI causes cognitive changes that are serious enough to be noticed by the person affected and by family members and friends but do not affect the individual's ability to carry out everyday activities
- **Amnestic MCI:** primarily affects memory
  - a person may start to forget important information that he or she would previously have recalled easily, such as appointments, conversations or recent events.
- **Nonamnestic MCI:** primarily affects thinking skills
  - including the ability to make sound decisions, judge the time or sequence of steps needed to complete a complex task, or visual perception.

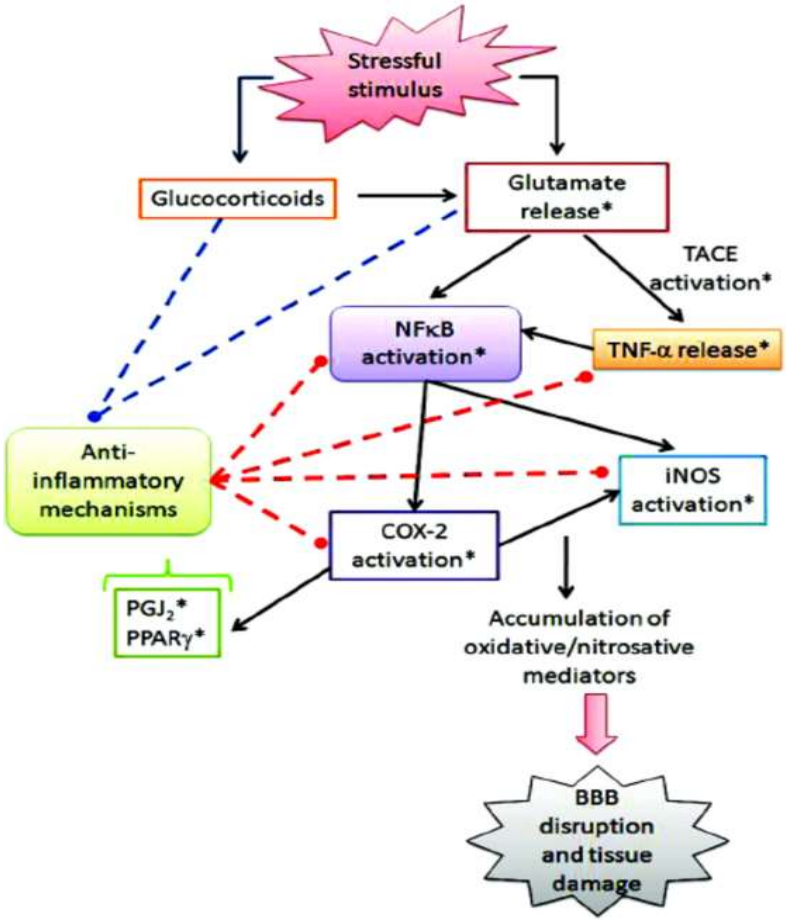
Prevalence of dementia and MCI





Lancet Public Health. 2020 Dec;5(12):e661-e671

Stress-induced neuroinflammation



Common causes of inflammation

- **S**tressors – mental, social, emotional, physical
- **T**oxins, toxicants, moulds, agrichemicals, petrochemicals (plastics)
- **A**ntigens, Allergens, Adverse food reactions
- **I**nfestations, Infections, Dysbioses
- **N**utritional excesses and deficiencies
- **S**leep disorders

IFM

Bredesen - Metabolic syndromes of Alzheimer's disease

- Type 1: Inflammatory ("Hot")
- Type 2: Atrophic ("Cold")
- Type 1.5: Glycotoxic ("Sweet" combines 1 & 2)
- Type 3: Toxic ("Vile")
- Type 4: Vascular ("Pale")
- Type 5: Traumatic ("Dazed")

Dietary Interventions

- Majority of the evidence indicates a Mediterranean diet reduces risk

Mol Psychiatry. 2015 Jul;20(7):860-6

- Emerging evidence suggest a Ketogenic diet has the potential to restore metabolic function including lipid and insulin sensitivity and may reduce cognitive decline

Nutrition. 2019 Apr;60:118-121

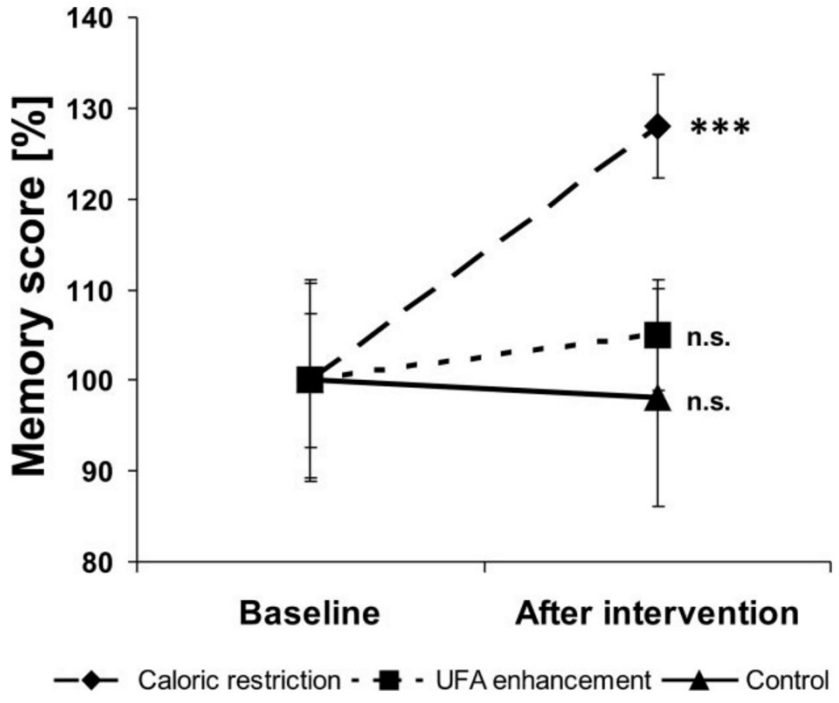
- Regular fish intake (or taking fish oil) shown to benefit cognitive performance and blood lipids in APOE e4 carriers

Neurology. 2016 May 31;86(22):2063-70

- Think real food – low stress diet

Calorie restriction

- RCT of 50 elderly on 30% calorie restriction for 3 months
- Decreases in fasting plasma levels of insulin and high sensitive c-reactive protein
- Significant increase in verbal memory scores



The effect of caloric restriction on working memory in healthy non-obese adults.
CNS Spectrums, 2019;*25*(1), 2-8.

Proc Natl Acad Sci U S A. 2009 Jan 27;106(4):1255-60


These smart pills are overpriced!
See, they're working!
PHARMACY

What Are Nootropics?

- Also known as “smart drugs”
- First used by Cornelius E. Giurgea in 1972 to describe substances that primarily activate cognitive functions, such as memory and learning, especially in situations where these functions are impaired
- The name consists of two Greek words: nöos, which means thinking, and tropein, which means to guide
- No uniform approach to categorizing these compounds
  - some authors distinguish between classical nootropics and substances that enhance brain metabolism
  - others combine these two groups, or use the term cognitive effect rather than nootropic

Nutrients 2022, *14*(16), 3367

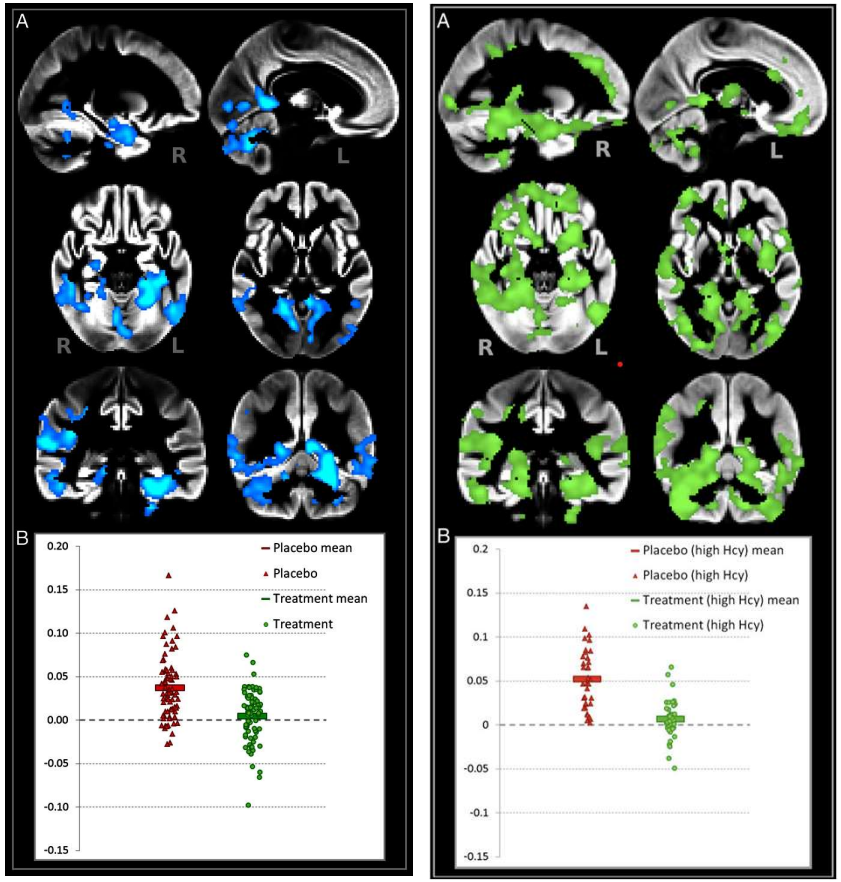
Mechanism of action

- Nootropics do not act directly by releasing neurotransmitters or as receptor ligands
- They positively affect neuronal protein and nucleic acid synthesis and stimulate phospholipid metabolism in neurohormonal membranes
- Some nootropics have been found to affect the elimination of oxygen free radicals, possess an anti-aggregation effect, and improve erythrocyte plasticity, which blood flow to the brain
- Nootropics are used in acute or subacute conditions for treating memory, consciousness, and learning disorders

Nutrients. 2022;14(16):3367

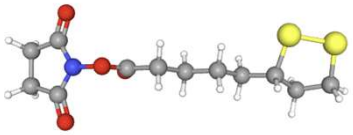
Preventing brain atrophy by B-vitamin treatment

- RCT of 156 participants using B-vitamin treatment (folic acid 0.8 mg, vitamin B6 20 mg, vitamin B12 0.5 mg) slowed shrinkage of the whole brain volume over 2 years
- B-vitamin treatment significantly reduces regional loss of GM ($P < 0.05$)
- Brain regions in blue demonstrate where B-vitamin treatment significantly reduces GM loss (A)
- Percentage of GM loss for those with high homocysteine (B)



Proc Natl Acad Sci U S A. 2013 Jun 4;110(23):9523

Alpha-Lipoic Acid (ALA)



- Sulfur-containing fatty acid naturally found in your body and is unique among most other antioxidants because it is both *water*- and *fat-soluble*
- You get small amounts of ALA in your diet from spinach and collard greens, broccoli, beef and organ meats
- ALA declines in your body as you age
- Supplementation can:
  - Increase the production of acetylcholine
  - Regenerate other depleted antioxidants (Vitamins C & E, glutathione)
  - Improve memory and learning ability, and restore the health of neurons
  - Boost cognitive performance and memory in Alzheimer's
  - Reduce brain damage after a stroke

Therapeutics. 2007 Jan;113(1):154-64
Toxicologic Pathology 2012 Sep;64(6):549-56
Journal of Neural Transmission. Supplementum.2007;72:189-93
General Pharmacology 1997 Sep;29(3):315-31
Brain Research. 1996 Apr 22;717(1-2):184-8

Alpha Lipoic Acid recommended dosage

- Taking ALA with a meal decreases it bioavailability
  - take on an empty stomach (1 hour before eating)
- Most ALA supplements contain a 50/50 mixture of *R-LA* and *S-LA* (S-LA is synthetic version of ALA, not found in nature and has little benefit)

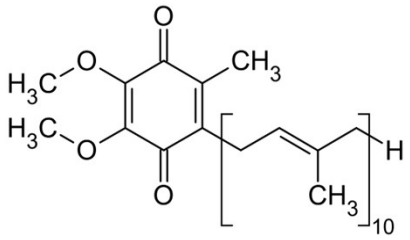
Clinical Pharmacology 2014; 6: 195-204

- Alpha-Lipoic Acid dosage for cognitive benefits is 200-600 mg per day
- ALA dosage for diabetic neuropathy is 800 mg per day divided into two doses
- Alpha-Lipoic Acid dosing for antioxidant benefits is 50-100 mg per day

Alpha Lipoic Acid Side Effects

- Side effects are generally rare, but can include diarrhoea, fatigue, insomnia and skin rash
- Can lower blood sugar levels and may need extra care in diabetics
- Can lower levels of thyroid hormone, good to check TFT's
- Can lower levels of vit B1 and consider taking extra
- Chemical structure of Biotin is similar to ALA and there is some evidence that ALA can compete with Biotin for transport across cell membranes

Coenzyme Q10



- Plasma CoQ10 found to be significantly associated to cognitive functioning and executive function

J Gerontol A Biol Sci Med Sci. 2022 Jul 31;glac152. doi

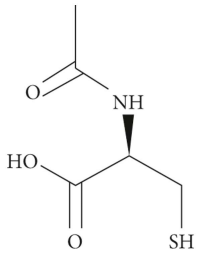
- Experimental studies in animal models suggest that CoQ10 may protect against neuronal damage that is produced by ischemia, atherosclerosis and toxic injury

CNS Spectr. 2007 Jan;12(1):62-8

- Co Q10 300mg + creatine 10g delayed cognitive decline in PD

Eur Neurol. 2015;73(3-4):205-211

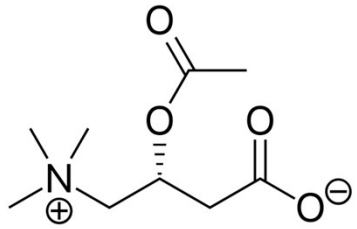
N-acetyl cysteine (NAC)



- NAC is a glutathione precursor and shows antioxidant, anti-inflammatory activities, pro-neurogenic and neuroprotective properties
- Autopsy studies show that patients with MCI and Alzheimer's disease have depleted glutathione levels in certain areas of the brain
- NAC has shown clear benefits in several animal models
  - Improved cognition in a mouse model of accelerated aging
  - Prevention of learning/memory impairment in mouse models of AD
  - Up to a 50% reduction in stroke infarct size along with a similar improvement in neurological function in rodent models of stroke
  - Significantly reducing motor dysfunction in a rat model of Parkinson's disease

Antioxidants 2020, 9, 260; doi:10.3390

Acetyl L-Carnitine



- Preclinical studies show improvement in energy status, decrease oxidative stress and can prevent subsequent cell death in models of adult, neonatal and pediatric brain injury

Neurochem Res. 2017 Jun;42(6):1661-1675

- Animal experiments suggest therapeutic potential for neuroprotection in a number of disorders including hypoxia-ischemia, traumatic brain injury, Alzheimer's disease

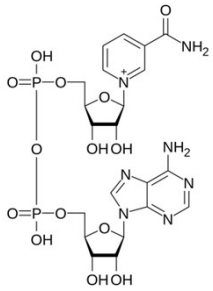
Neurochem Res. 2017 Jun;42(6):1661-1675

- A meta-analysis of 21 studies conducted in patients with MCI to found that ALC was effective in improving cognitive performance
  - highest efficacy was in memory and intellectual functions
  - dose range of 1.5 to 2 g/day

Psychopharmacol. 2003;18:61–71

- Usually well tolerated but can cause nausea, vomiting, depression, mania, confusion, and aggression in AD patients

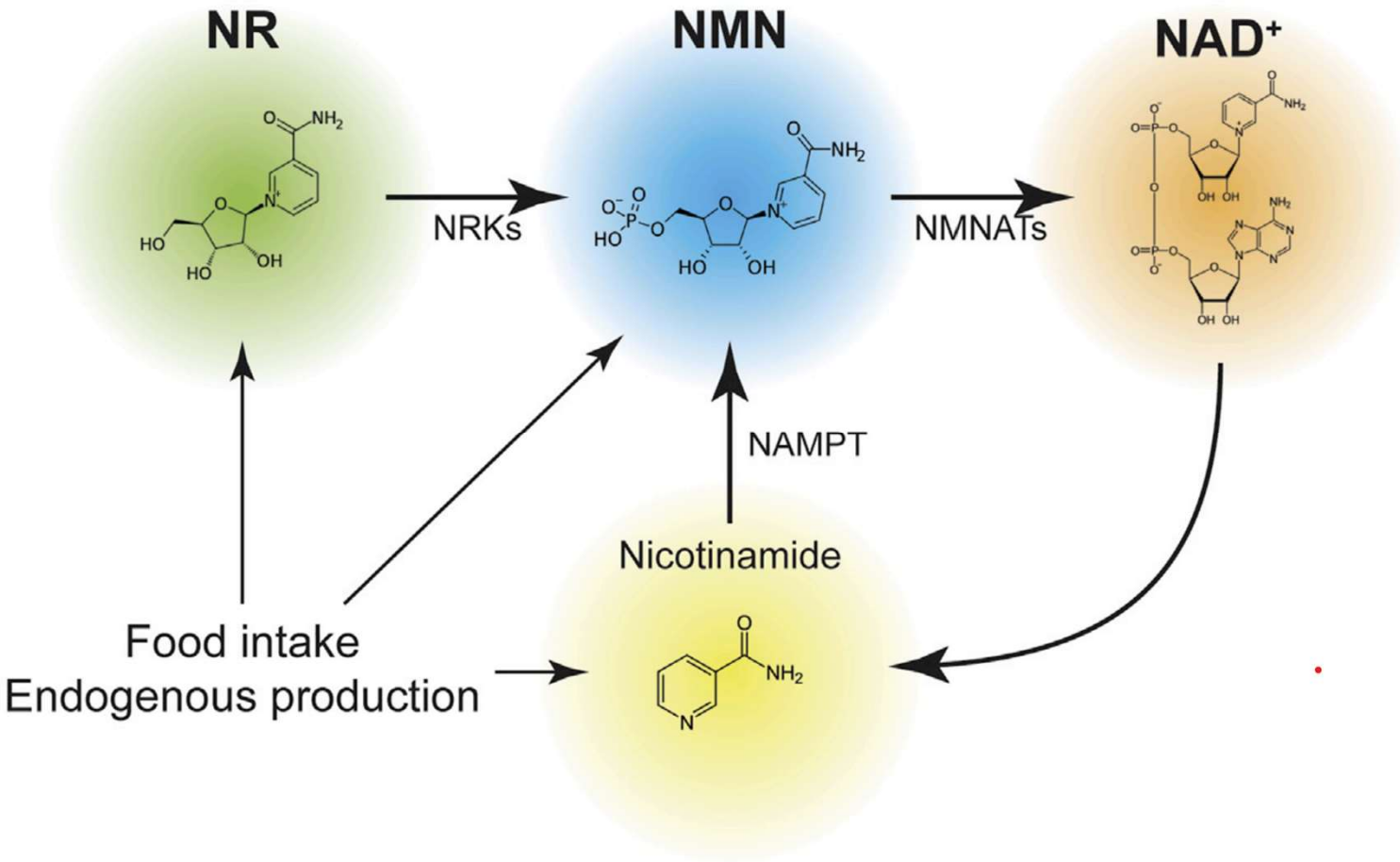
Nicotinamide adenine dinucleotide (NAD^+)



- NAD+ is fundamental to cellular energy metabolism, via electron exchange from tricarboxylic acid (TCA) cycle for the generation of ATP by oxidative phosphorylation
- Key substrate for for ADP-ribosylation, protein deacetylation by sirtuins, and cyclic ADP-ribose production
- Preservation of cognitive ability by increasing NAD^+ levels with precursors is promising for age-related cognitive decline (including Alzheimer's disease and vascular dementia), diabetes, stroke, and traumatic brain injury
- Supplementation with NAD^+, NADH, nicotinamide (NAM), nicotinamide mononucleotide (NMN), nicotinamide riboside (NR), and niacin (or nicotinic acid)

Nutrients. 2022 Aug 7;14(15):3231

NAD^+ production

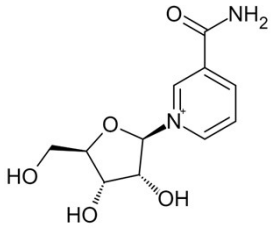


NAD^+

Disease	Findings
Dementia	• Preclinical research suggests NAD^+ precursors could be effective for different forms of dementia. • Head-to-head comparisons of different precursors (NR, NMN, NAM, niacin) are lacking. • Work is needed to investigate the safety and effectiveness of prophylactic supplementation with NAD^+ precursors in people at risk of age-related cognitive decline.
Diabetes	• Animal models support the conclusion that NAD^+ precursor supplementation could improve the long-term cognitive health of people with diabetes, although clinical trials are needed. • Investigation is needed on the impact of routine supplementation with NAD^+ precursors on cognitive impairment resulting from an event of severe hypoglycaemia.
Stroke	• Animal studies support the conclusion that treatment with NAD+ precursors could improve cognitive recovery after stroke. • The effect of supplementation prior to ischemic injury has not been investigated.
Traumatic brain injury	• Almost all work on TBI has focused on supplementation with NAM. • Effects have been inconsistent, with some studies reporting negative impacts on cognitive health. • This field of inquiry now appears inactive.

Nutrients. 2022 Aug 7;14(15):3231

Nicotinamide riboside (NR)



- Leading candidate due to its bioavailability, safety, and strong ability to raise NAD^+ content compared to other precursors
- Better pharmacokinetic and pharmacological properties
- Animal studies have reported that equimolar oral NR is superior to NA and NAM in elevating NAD^+ content in the liver
- NR was confirmed across a number of studies as well-tolerated, up to 2 g of a daily dose, and was not found to be associated with flushing or any severe side-effects

Nutrients. 2020 Jun; 12(6): 1616

Other Nutrients

- Phoshatidyl serine – small RCT's showing positive effects

  Europ Neuropsychopharm. 1992; 2(2),149-155;
  Acta Neurol Scand. 1986; 73(2), 136 - 140

- Glycerophosphocholine - Improves acetyl choline
  Review of 13 trials (n=4054) showed tendency for cognitive improvement

  Mech Ageing Devel. 2001; 122(16) 2041-2055

- Astaxanthin possible neuroprotective effect re antioxidant potential and mitochondria protection *Forum Nutr.* 2009;61:129-35

- Vincopine may protect neurons against oxidative stress

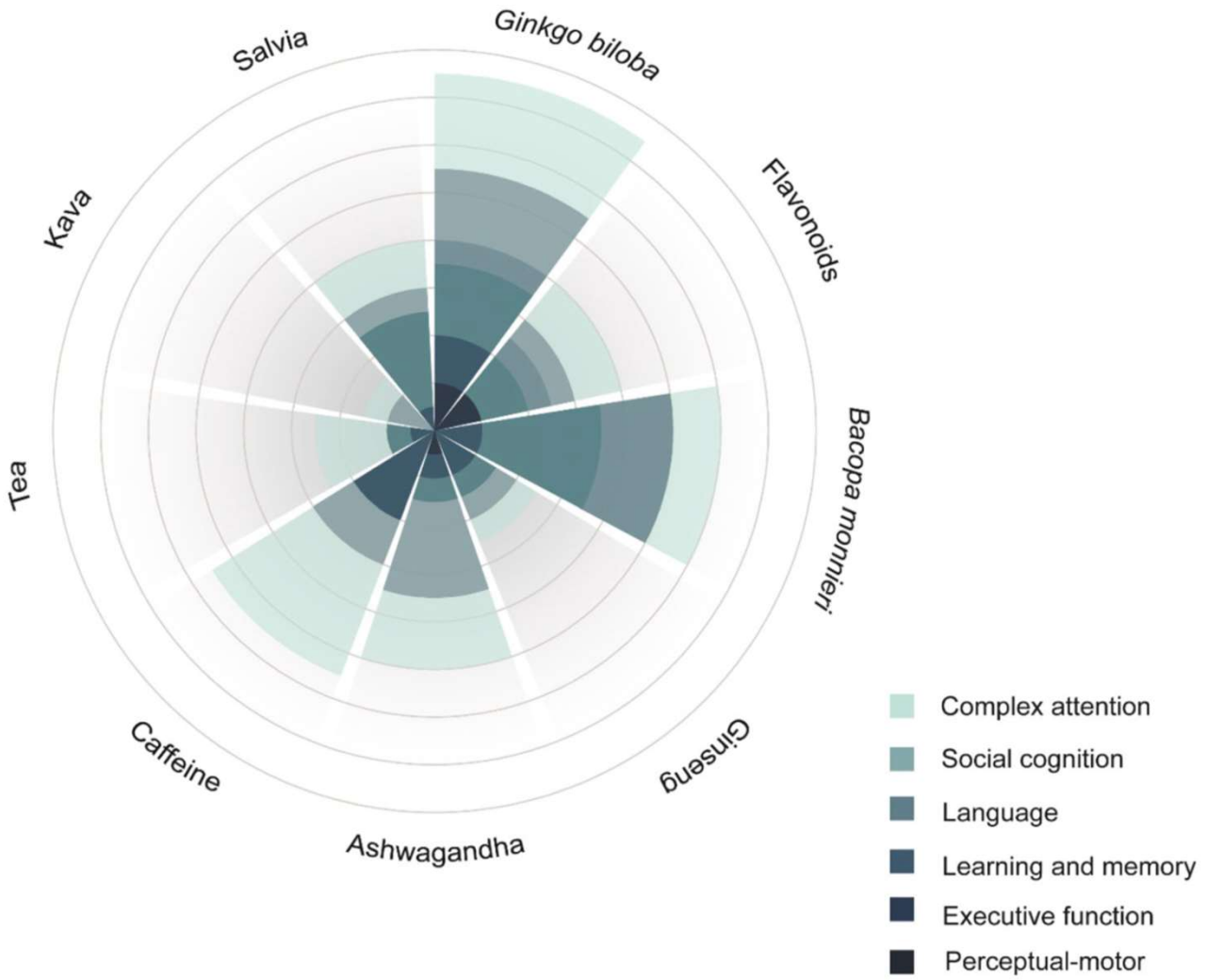
  Nutrition. 2003;19(11-12):957-75

- S-adenosylmethionine (SAMe) low in a group with AD

  J Neurol Neurosurg Psychiatry. 1990; 53(12): 1096–1098

Herbs

Evidence rating of the main nootropics



Crit Rev Food Sci Nutr. 2022 Jan 3;1-25

Ginkgo biloba

- Effective at increasing blood flow to the brain and enhancing vascular permeability *J Environ Sci Health C Environ Carcinog Ecotoxicol* Rev. 2007 Jul-Sep;25(3):211-44
- Improves blood viscosity *Clin Nutr.* 2004 Aug;23(4):615-21
- Seems to protect against neuronal damage *Proc Natl Acad Sci USA* 2004;99:12197-12202
- Reduces the intensity and impact of tinnitus and dizziness in elderly individuals with MCI *Clinical Interventions in Aging 2018;*13:1121–7
- 40 mg taken three times daily positively modulated mood, memory, information learning and working capacity in young adults with cognitive impairment symptoms, including headache and memory and attention impairments
  Zh Nevrol Psikhiatr Im S S Korsakova. 2014;114(6):38-41
- Caution with drugs (warfarin, cyclosporin, antidepressants)

Review of RCT's of cognitive function of *Ginkgo biloba* extract (EGb)

Concluded that Ginkgo may improve cognitive function in mild dementia during long-term administration (>24 weeks) and appropriate dosage (240 mg per day)

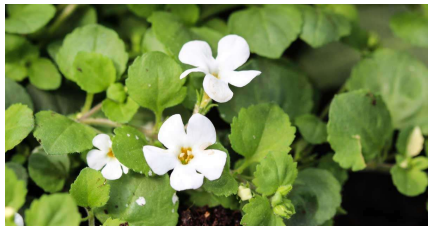
No	Consensus statement	Concrete content
1	Efficacy of EGb 761® in AD, VaD, and BPSD	Best practice for the pharmacological treatment as follows: AD: AChEI, memantine, EGb VaD: AChEI, memantine, EGb, antiplatelet therapy BPSD: ChEI, nonpharmacological treatment, antipsychotics (off-label), memantine, SSRIs, sedatives, and EGb
2	Management of MCI	EGb may be considered for use in patients with MCI
3	How to use EGb	EGb can be used as a single agent, and allow sufficient time to take effect
4	The dosage	EGb at daily dose of 240 mg
5	Lack of efficacy or intolerance of standard drugs may warrant use of EGb	EGb was recommended to treat AD, VaD, and mixed dementia, when the patients unable to tolerate the side effects of standard treatments
6	Adjunctive therapies	EGb was one of the key management options adjunctive to standard pharmacological therapy for AD, VaD, and BPSD
7	Management of comorbidities	EGb played an important role in the management of co-morbidities, such as hypertension, in patients with AD, VaD, and BPSD
8	Does not appear to prevent dementia	EGb was not recommended for prevention of dementia
9	Well tolerated	EGb had a good tolerability profile in the treatment of MCI, AD, VaD, and BPSD
10	No overall increased bleeding risk	EGb appeared to be no overall added risk of bleeding
11	No significant interaction with anticoagulants or antiplatelet agents	EGb had been demonstrated no significant interaction with anticoagulants and antiplatelet agents

Front Pharmacol. 2020 Feb 21;10

Ashwagandha (*Withania somnifera)*

- Systematic review showed improved performance on cognitive tasks, executive function, attention, and reaction time Phytother Res. 2020 Mar;34(3):583-590.
- May be effective in enhancing both immediate and general memory in people with MCI as well as improving executive function, attention, and information processing speed J Diet Suppl. 2017 Nov 2;14(6):599-612.
- Antistress adaptogenic activity of ashwagandha has also been described as reducing stress-induced physical effects, along with reduced cortisol, in RCT *Cureus*. 2019;11(12):e6466.
- It also appears to be well tolerated, with good adherence and minimal side effects Phytother Res. 2020 Mar;34(3):583-590.

Brahmi
(Bacopa monnieri)



- 52 active compounds identified and their associated 780 direct receptors
  Biomolecules 2020, *10*(4), 536
- Promotes free radical scavenger mechanisms and protects cells in prefrontal cortex, hippocampus, and striatum against cytotoxicity and DNA damage implicated in AD
  Ann Neurosci 2017;24:111–122
- Also reduces lipoxygenase activity reducing lipid peroxidation, increases glutathione peroxidase and chelates iron
  Ann Neurosci 2017;24:111–122
- 6 RCT's have shown clear nootropic activity on free recall memory
  J Altern Complement Med. 2012 Jul;18(7):647-52
- 640 mg daily in healthy subjects significantly improved performance in divided attention tasks
  J Altern Complement Med. 2012 Jul;18(7):647-52
- Systematic reviews have also reported variable or inconclusive results

Bacopa clinical trials and systematic reviews

Study	Dose	Time	Participants	Effect	Reference
Systematic Review (n = 6) R PC trials	300–450 mg/d, 3 different extracts	12 weeks	Adult humans without dementia or significant cognitive impairment.	Improvement in memory free recall. Evidence for enhancement in other cognitive abilities currently lacking.	(Pase et al. 2012)
Open label clinical trial	225 mg/d BacoMind®	4 months	28 low IQ (70–90) children	Enhancement of working memory, short term verbal memory, logical memory, memory related to personal life, visual and auditory memory.	(Usha et al. 2008)
R PC DB	300 mg/d (150 mg twice/d)	6 weeks	60 medical students (19–22 years)	Improvement in learning, memory, executive function and attention tasks.	(Kumar et al. 2016)
DB PC independent-group design	300 mg/d CDRI 08 extract	5 and 12 weeks	46 healthy (18–60 years)	Improved speed of visual information (IT task), learning rate and memory consolidation (AVLT), and state anxiety, with maximal effects after 12 weeks.	(Stough et al. 2001b)
R DB PC	450 mg/d BacoMind®	12 weeks	65 elderly with memory complaints (50–75 years).	Enhancement in attention and verbal memory: digit span backward, list learning delayed recall, paired associates dissimilar delayed recall and visual retention-I tests.	(Barbhaiya et al. 2008)
R DB PC	300 mg/d whole plant dry extract	12 weeks	48 healthy elderly (65 or older, mean age 73.5 years)	Improved AVLT delayed word recall, Stroop test, CESD-10 depression and anxiety scores, and decreased heart rate. No effects on the DAT, WAIS digit task, mood, or blood pressure. No significant effect on memory after 12 weeks of administration.	(Calabrese et al. 2008)
DB PC crossover	320 mg/d and 650 mg/d CDRI 08 extract	Acute	24 healthy (18 to 56 years)	320 mg (not 650 mg) CDRI 08 improved performance in the Cognitive Demand Battery.	(Downey et al. 2013)
Review (11 R DB PC)	At least 200 mg/day	12 weeks to 12 months	Healthy subjects and AD patients	Moderate improvement of logical memory.	(Brimson et al. 2021)
R DB, parallel Phase-2 study	300 mg/day vs. donepezil 10 mg	12 months	48 patients (>50 years), diagnosed with MCI-AD or AD	No significant differences after 12 months of treatment	(Prabhakar et al. 2020)
Review	bacosides and bacopa saponins	–	–	Toxicity of Bm needs to be adecuately investigated in populations such as children, pregnant, lactating, elderly. Proper chemical characterization needs to be expanded besides bacoside A.	(Banerjee et al. 2021)

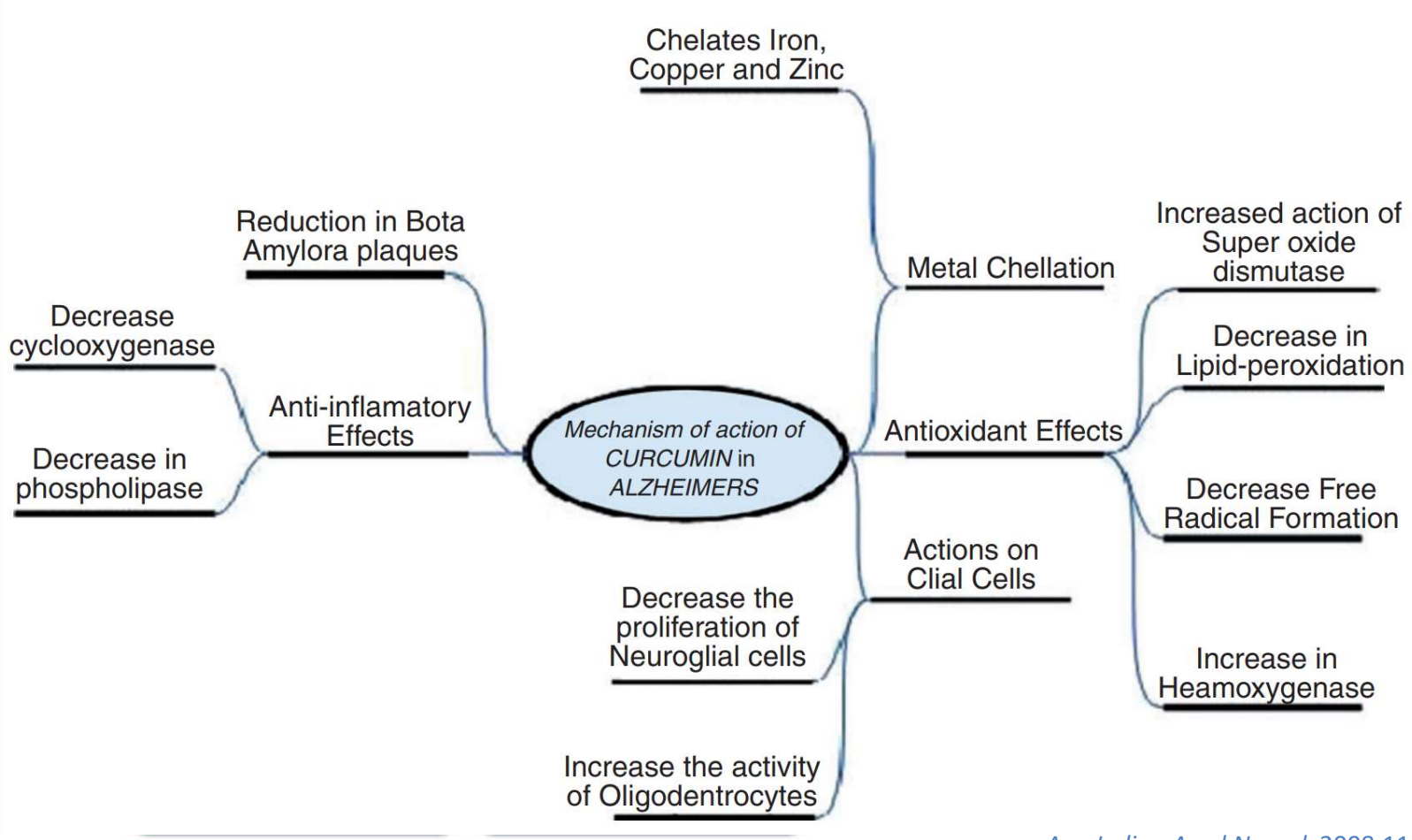
R: randomized; DB: double blind; PC: Placebo controlled; IT task: measures speed of visual information processing, AVLT: Auditory Verbal Learning Test, CESD-10: Center for Epidemiologic Studies Depression scale, DAT: Divided Attention Task, WAIS: Wechsler Adult Intelligence Scale.

Crit Rev Food Sci Nutr. 2022 Jan 3;1-25

Curcumin

- Polyphenol with strong antioxidant and anti-inflammatory effects that has been shown to be effective in ameliorating cognitive decline in animal studies
- Notable antidepressant and anxiolytic abilities Phytother Res. 2020 Apr;34(4):896-903
- Curry consumption related to significantly better MMSE scores in population-based cohort (*n* = 1,010) *Am. J. Epidemiol.* 2006;164 (9): 898-906
- Meta-analysis of 8 RCT's showed an improvement in working memory and a borderline benefit in processing speed *Pharmaceuticals (Basel)*. 2021;14(12):1235.

Mechanisms of action of curcumin in AD



Ann Indian Acad Neurol. 2008;11(1):13-19

Lion's mane
(Hericium erinaceus)

- Induces nerve growth factor (NGF) which is essential for the maintenance of the basal forebrain cholinergic system
  Int J Med Mushrooms. 2013;15(6):539-54
- Increases brain-derived neurotrophic factor (BDNF) and synaptophysin (SYP) in cell culture
  Bioorg Med Chem Lett. 2021 Jan 1;31
- RCT with 50- to 80-year-old Japanese men and women diagnosed with MCI
  - 250 mg tablets containing 96% of lion's mane dry powder 3/day for 16 weeks
  - At weeks 8, 12 & 16 lion's mane showed significantly increased scores for cognitive function
  - 4 weeks after stopping treatment, cognition scores decreased significantly

  Phytother Res. 2009 Mar;23(3):367-72
- RCT of 68 MCI patients given 350 mg lion's mane capsules for 49 weeks
  - demonstrated higher CASI, MMSE, and IADL scores
  - reduced structural deterioration in the ARC and PHC regions on MRI
  - Improved blood markers (Hb, Hcy, SOD, BDNF, and albumin)

  Front Aging Neurosci. 2020;12:155

Sage
(*Salvia Officinalis*)

- Terpenoids contained in sage extracts possess cholinesterase-inhibiting abilities
- In RCT, 50 µL of the essential oil) enhanced immediate word recall in healthy young subjects and improved the speed of memory *Physiology & Behavior* 2005;83 (5):699–709
- Significant improvement in secondary memory was reported after the administration of 333 mg of sage extract in healthy older adults (>65 years of age)

  Psychopharmacology 198 (1):127–39.
- RCT of subjects with mild to moderate AD, long-term treatment with sage essential oil over 4 months significantly improved scores on the Alzheimer's Disease Assessment Scale (ADAS-cog) and Clinical Dementia Rating (CDR)
  - Also seemed to reduce agitation in AD subjects

  J Clin Pharm Ther. 2003 Feb;28(1):53-9

Huperzine-A
(Chinese club moss - *Huperzia serrata*)

- Sesquiterpene alkaloid compound which acts a reversible acetylcholinesterase
  - stronger penetration in blood brain barrier, prolonged duration and greater bioavailability than other cholinesterase inhibitors (donepezil, rivastigmine, and tacrine)
  - reduction of IL-1β, IL-6, TNF-α, and NF-kB signaling preserves neuronal function

Molecules 2021, 26(21), 6531

- Meta-analysis of 10 RCTs of Huperzine A in Alzheimer's disease (AD) and vascular dementia (VD)
  - Significantly improved cognitive status (MMSE) & activities of daily living in AD & VD patients

Evid Based Complement Alternat Med. 2014;2014:363985

Gotu kola
(Centella asiatica)

- Anti-oxidative & anti-inflammatory properties, neuron regenerative ability, potential for neuron damage prevention, neurotoxicity inhibition, anti-anxiety and anti-depressive properties, AChE inhibitory potential and ability to reduce accumulation of amyloid plaques *Trends in Food Science & Technology.* 2018;79:88-97

- Asiaticoside, a major active constituent of gotu kola, has been reported as an agent to treat dementia and a cognitive enhancer *Molecules*. 2012;17(9):10503–10539

- RCT of 6 weeks treatment with gotu kola 750 mg and 1000 mg appeared to improve all cognitive domains in patients with cognitive impairment following strokes *Evid Based Complement Alternat Med*. 2016;2016:2795915

- RCT in women with MCI showed that 20 weeks of gotu kola 500mg/day is effective in increasing semantic fluency and visual memory *IOP Conf. Ser.: Earth Environ. Sci.* 2021;755,012064

Prescription nootropics

- Memantine
- Modafinil
- Deanol (DMAE)
- Meclofenoxate
- Nicergoline
- Pyritinol
- Naftidrofuryl
- Dihydroergotoxine
- Racetams

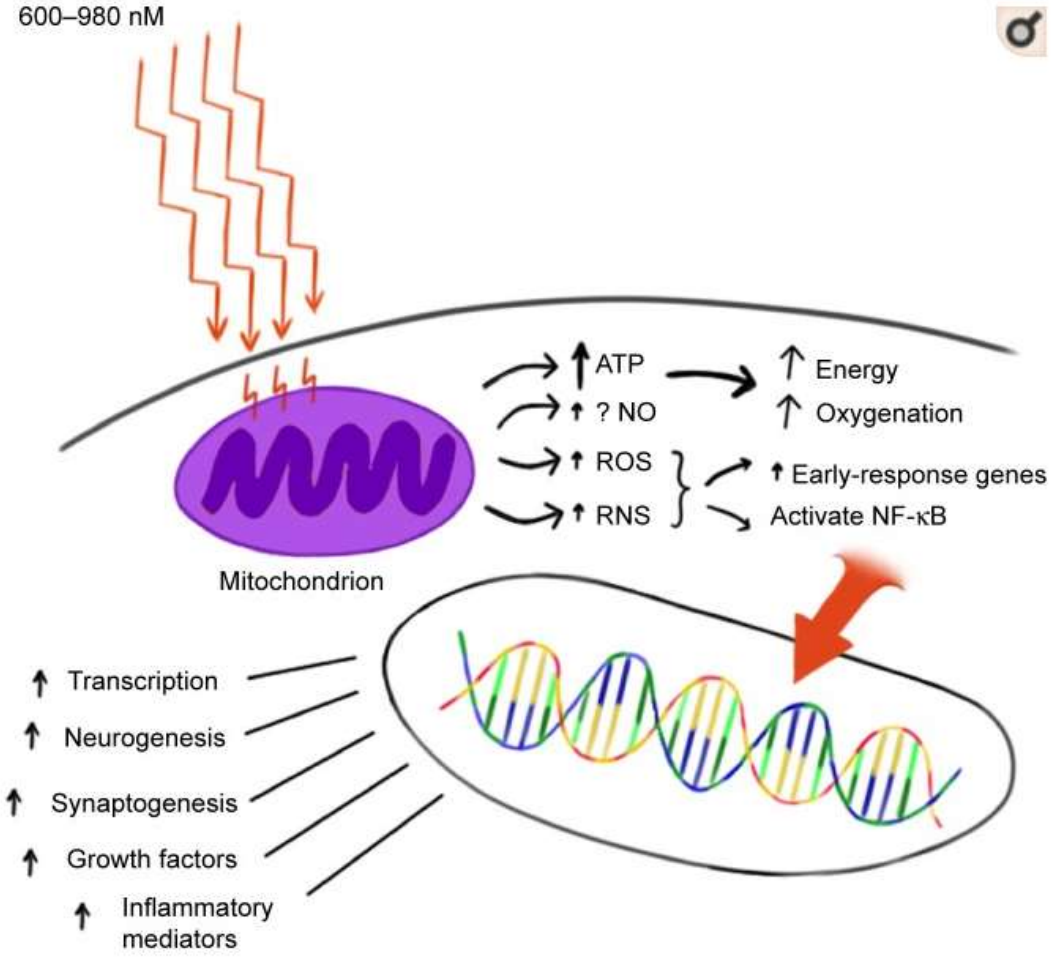
Nutrients. 2022;14(16):3367
Pharmaceuticals. 2022;15(9)

Prescription nootropics

- Racetams
  - mode of action is not well defined but appear to have differential effects on subtypes of glutamate receptors, but not GABAergic actions *Drugs.* 2010;70(3),287-312
  - Piracetam
    - Meta-analysis showed compelling evidence for the global efficacy of piracetam in a diverse group of older subjects with cognitive impairment *Dement Geriatr Cogn Disord*. 2002;13(4):217-24
  - Pramiracetam
    - RCT of 400 mg pramiracetam sulphate TID in males with TBI indicate that measures of memory, especially delayed recall, had clinically significant improvements *Brain Inj*. 1991 Oct-Dec;5(4):375-80.
  - Phenylpiracetam
    - RCT of 400 mg/day for 1 year after stroke in 200 patients and found that restoration of neurologic and daily living activities was significantly ($p < 0.0001$) better Zh Nev Psi Im S S Kor. 2010;110(12 Pt 2):38-40
  - Aniracetam
    - Open-label study of 276 patients with dementia given 1500 mg daily and found it preserved all neuropsychological parameters for at least 12 months, and favorable effect on emotional stability

      CNS Neuroscience & Therapeutics18(2012) 302–312

Laser



Some secondary mechanisms of action:

- NO as neurotransmitter
- Increased electron transport chain activity
- Cell proliferation genes activated
- ROS related genes are activated
- Growth Factors increased: NGF, BDNF, TGF-B, VEGF
- Increased Neurogenesis

Neuropsychiatr Dis Treat. 2015; 11: 2159–2175

NIR Laser in animal model of TBI

- single dose of 800–810 nm NIR gave 50% reduction in volume of TBI lesion at 4 weeks
- daily applications for 3 days gave much greater neurological benefit
  - smaller lesion size
  - fewer degenerating neurons
  - more proliferating cells
  - greater levels of brain-derived neurotrophic factor

Neuropsychiatr Dis Treat. 2015; 11: 2159–2175

NIR laser in human trials

- Case series of 10 chronic TBI patients
  - course of 10 treatments with 15W, 810nm laser
  - all patients experienced significant clinical improvement
    - headache, insomnia, depression, anxiety, cognition, QOL and return to work
  - improvements persisted at 6/12 follow up

Neuropsychiatr Dis Treat. 2015; 11: 2159–2175

- Case series of 11 chronic mTBI patients
  - improved cognitive function and sleep, and less PTSD

J Neurotrauma. 2014 Jun 1;31(11):1008-17

- Case series of 12 war-veterans with TBI
  - 20 minute laser diode treatments x 3/week for 6 weeks
  - significantly improved neuropsychological scores
  - improved blood flow on SPECT scans

Photomed Laser Surg. 2018 Nov 28. doi: 10.1089

Photobiomodulation Improves Cognitive Function

- RCT of 30 older adults without a neuropsychiatric history
  - performed cognitive tests of frontal function before and after a single 7.5-min session of real or sham PBM
  - 3 light-emitting diode cluster heads (633 and 870 nm) applied to forehead and posterior midline, and delivered a total energy of 1349 J
  - only those who received real PBM exhibited significant improvements in their action selection, inhibition ability, and mental flexibility

Int J Geriatr Psychiatry. 2019 Feb;34(2):369-377

- RCT of 11 patients diagnosed with dementia
  - 28 consecutive, six-minute transcranial sessions of NIR PBM using 1060–1080 nm LEDs embedded in a helmet
  - improvement in executive function, clock drawing, immediate recall, praxis memory, visual attention and task switching

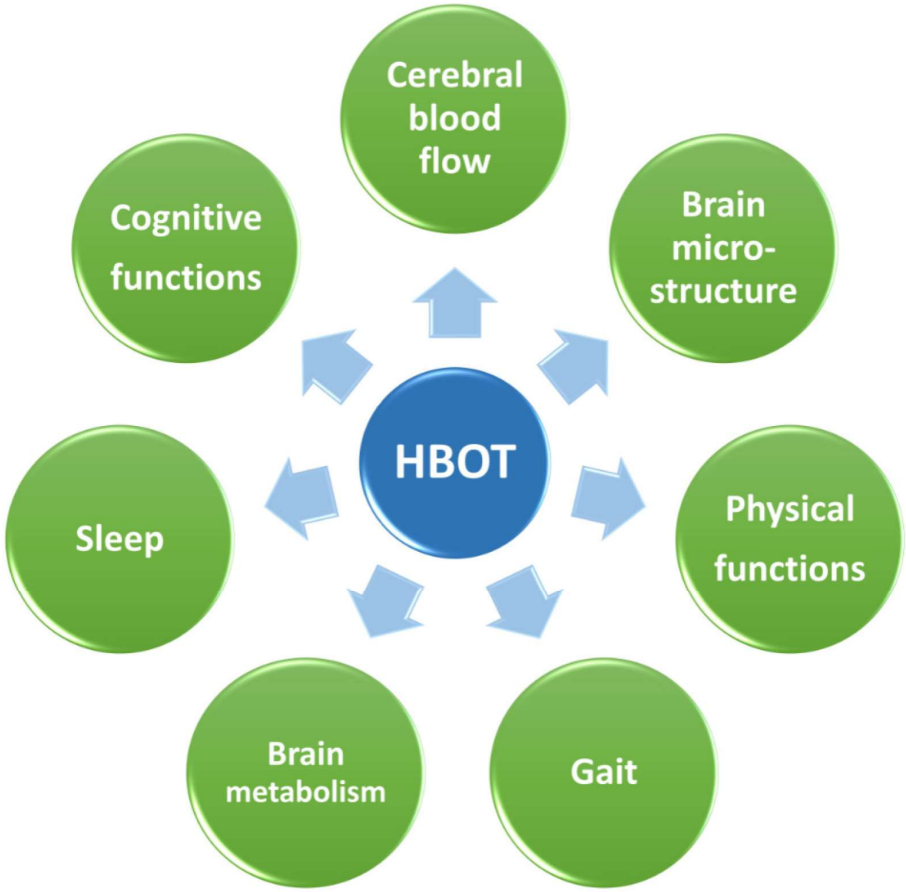
J Neurol Neurosci. 2017;8(1):176.

Infrared laser – 15W, 810/980nm

Low-level laser therapy

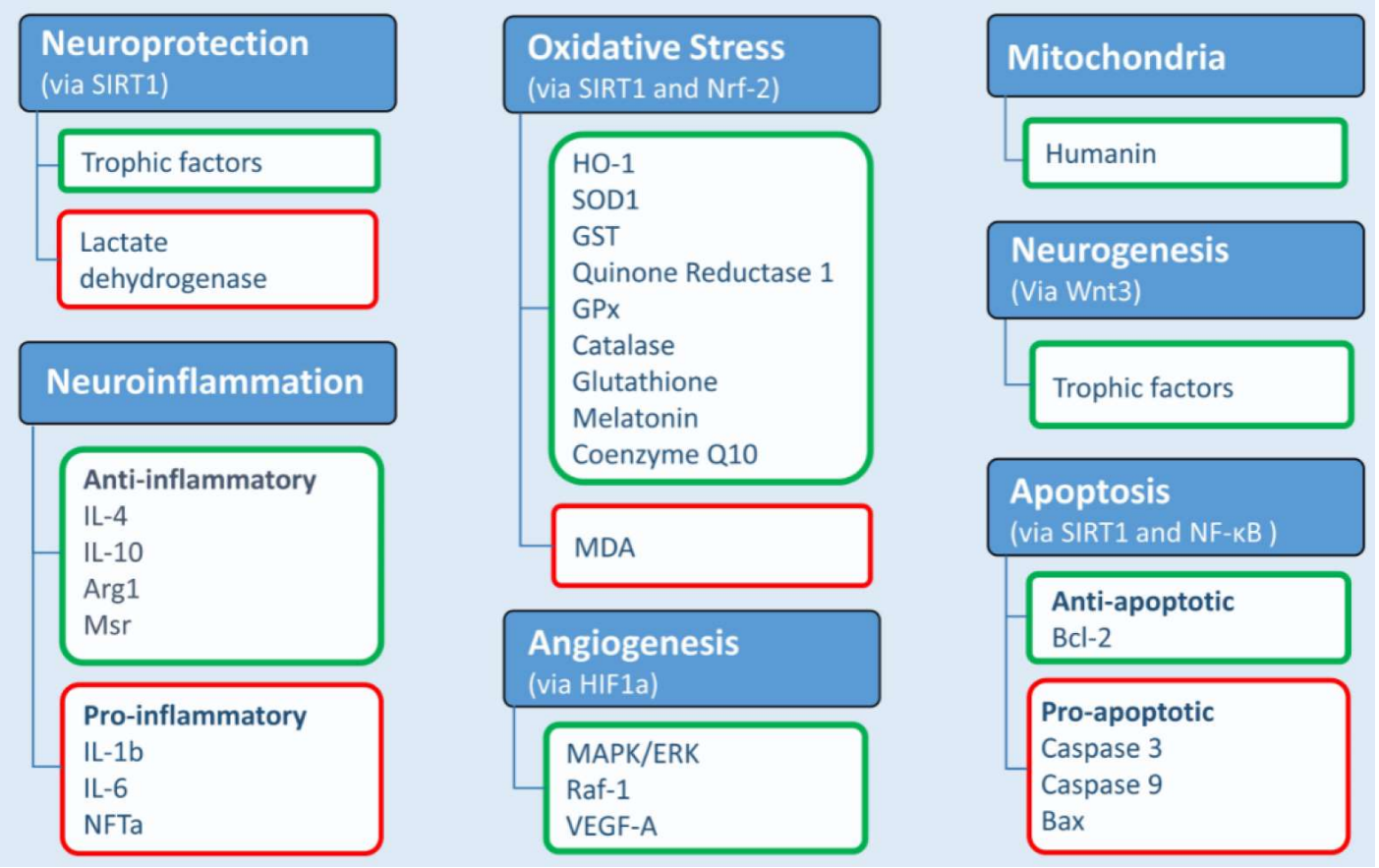
HBOT for neural recovery

HBOT



Biomolecules. 2021 Oct 15;11(10):1520

HBOT metabolic mechanisms



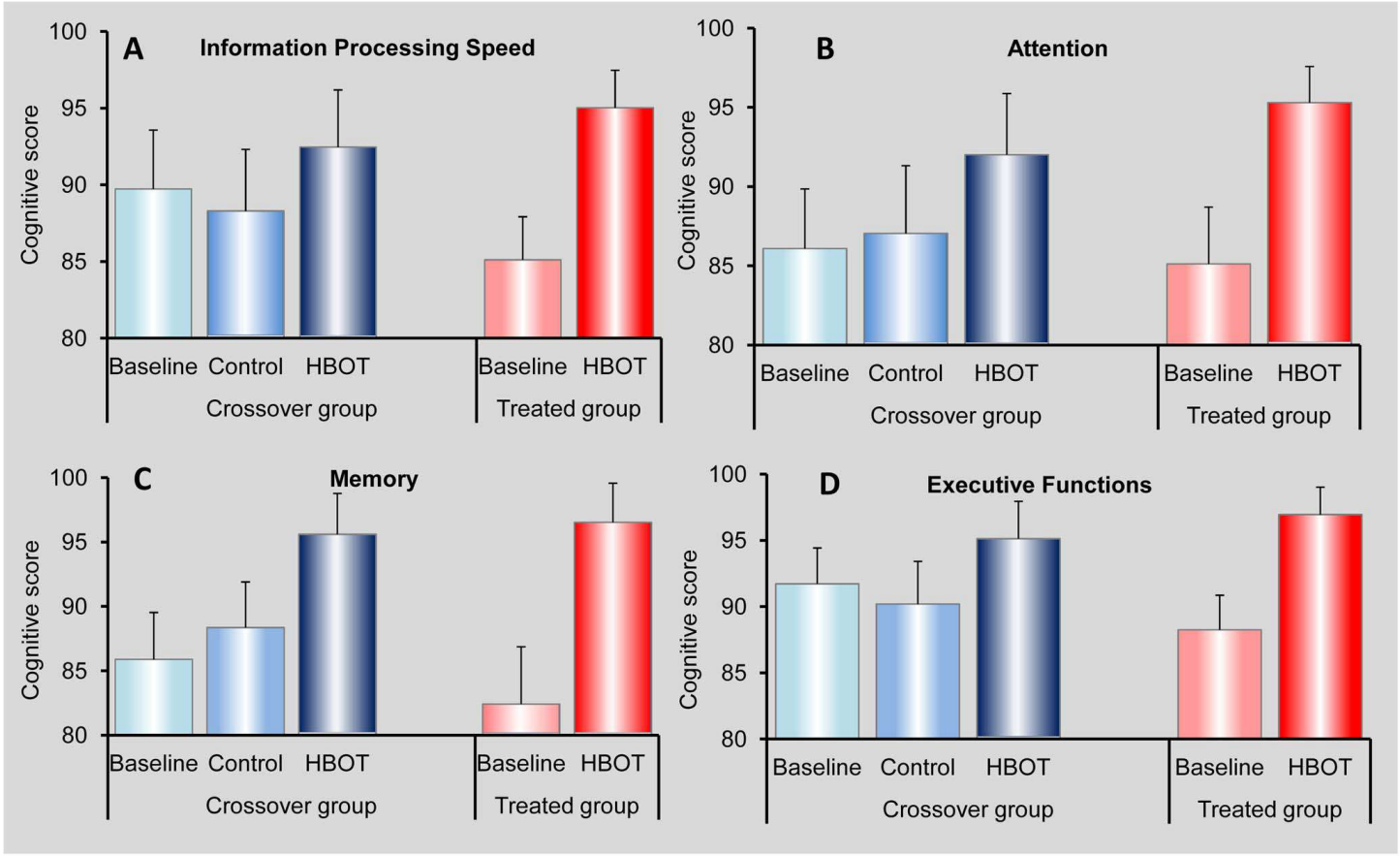
Biomolecules. 2021 Oct 15;11(10):1520

HBOT for TBI

- 56 mTBI patients 1–5 years after injury with prolonged postconcussion syndrome
- prospective, randomized, crossover controlled trial
- 40 HBOT sessions, 60 minutes of 100% O2 at 1.5 ATA
- significant improvements in cognitive function & QOL
- SPECT imaging revealed elevated brain activity in good agreement with the cognitive improvements

PLoS One. 2013 Nov 15;8(11):e79995

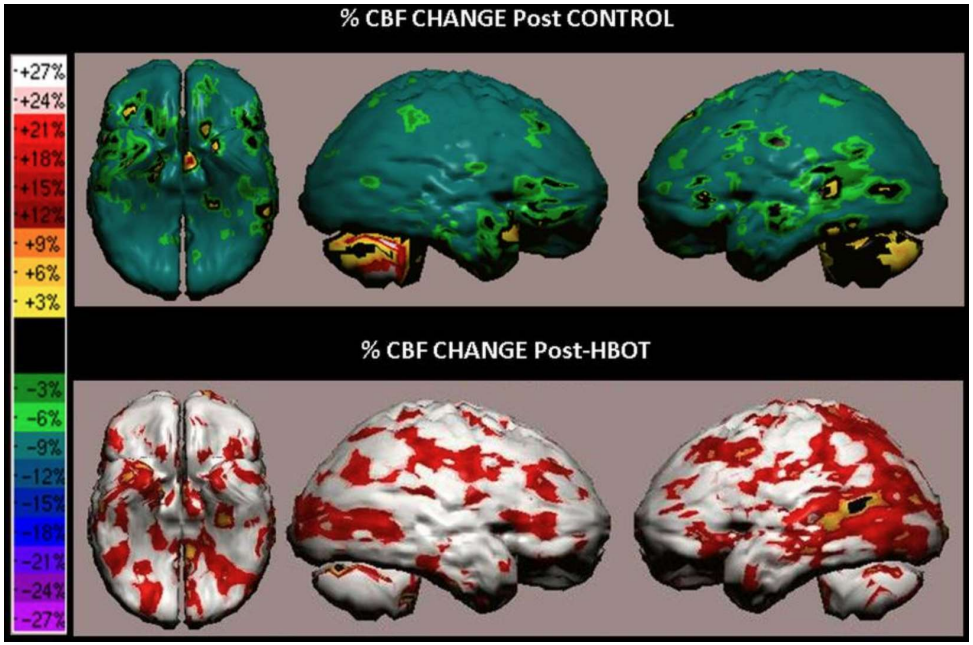
Changes in cognitive function with HBOT



PLoS One. 2013 Nov 15;8(11):e79995

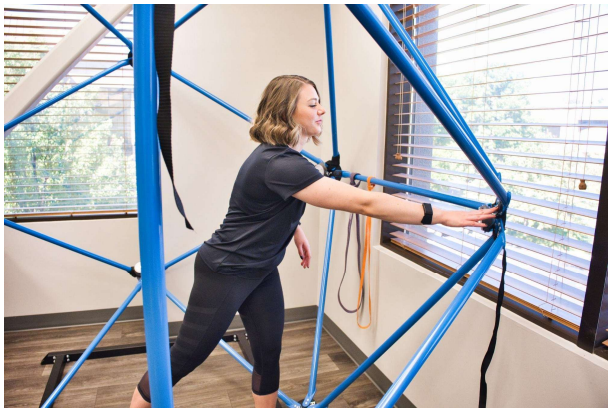
HBOT perfusion changes in TBI

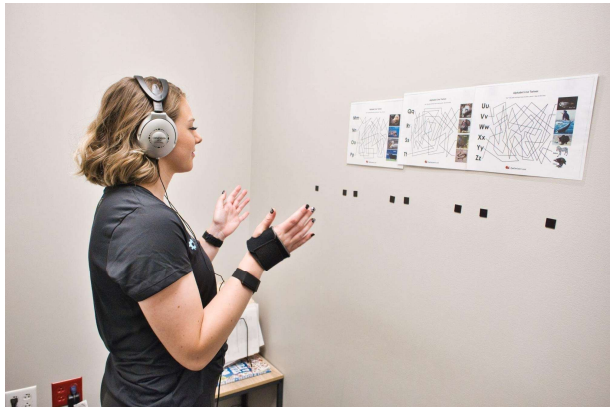
- Brains SPECT perfusion maps showed most improvement in:
  - Frontal Lobes (BA 45-46=DLPFC) = *executive function*
  - Frontal Lobes (BA 11)+Orbitofrontal cortex = *emotional control*
  - Anterior Temporal Lobes (BA38) = *speech comprehension, and naming*
  - BA 39 (angular gyrus/parietal) = *self awareness/theory of mind*

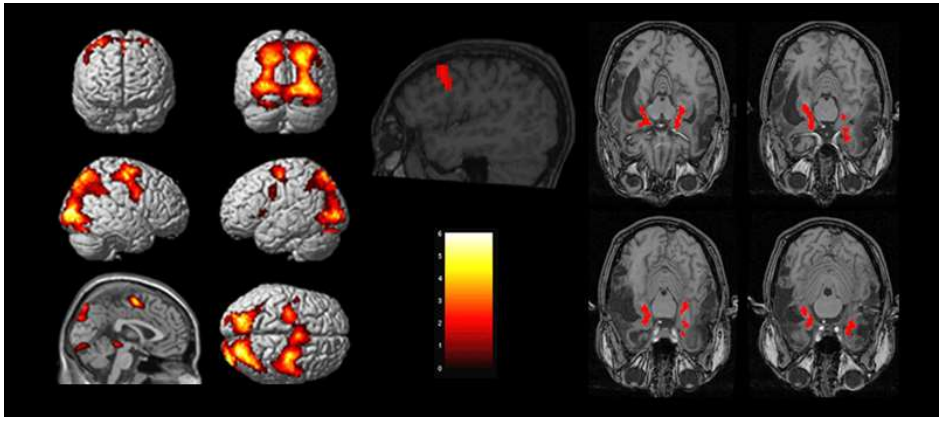


PLoS One. 2013 Nov 15;8(11):e79995

Neuroplasticity Treatment Exercises







Neurofeedback for TBI

- A comprehensive review of 22 neurofeedback TBI articles found that all reported benefit to the patients
  - However, none of these were randomized, placebo controlled or double-blind
  - Main areas of improvement included improvements in attention, impulse control, and processing speed
  - Some studies showed improvements in QEEG variables

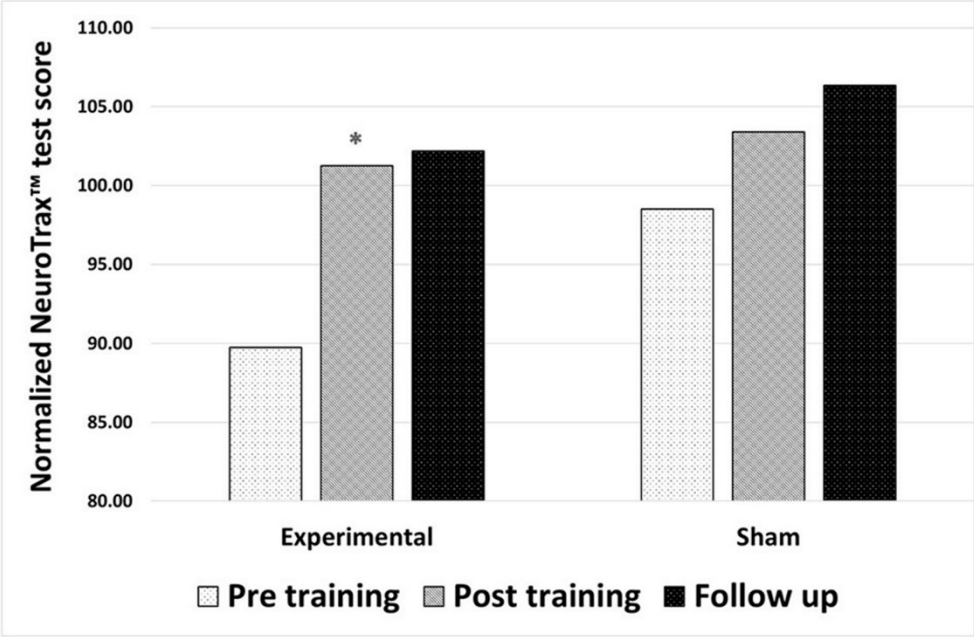
Ann Clin Psychiatry. 2013 Nov;25(4):289-96-8

- TBI may benefit from improved motivation and some reduction of symptoms related to attention, mood, and mindfulness

Med Acupunct. 2017;29(4):215-219

Neurofeedback for MCI

- RCT of 15 patients and 15 control
- Promising and affordable novel approach for treating the decline in memory witnessed in patients with MCI



Front Aging Neurosci. 2021; 13: 657646

Summary

- Diet
  - Mediterranean, ketogenic, low stress diet
- Nootropics
  - Alpha lipoic acid, acetyl l-carnitine, Co Q10, nicotinamide riboside, phosphotidyl choline, vincopine
  - Ginkgo, Bacopa, Ashwagandha, Curcumin, Lions mane, Gotu kola, Sage Chinese club moss
  - Prescription drugs, memantine, modafinil, racetams, etc
- HBOT
- Photobiomodulation
- Neural therapies