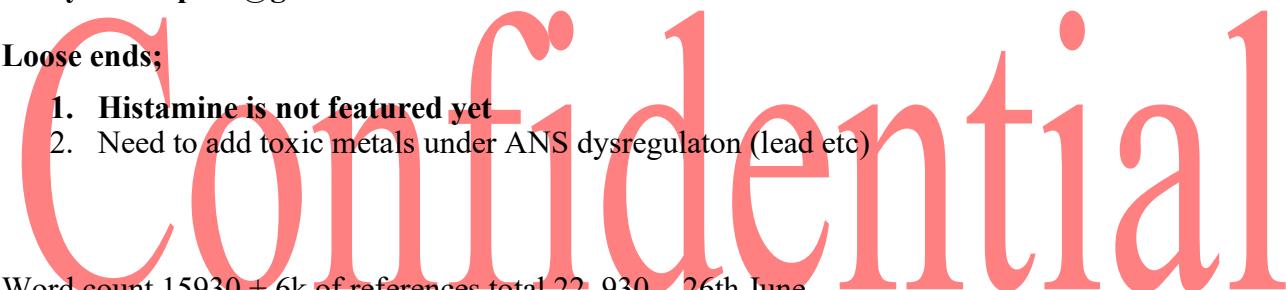


1 **Nutritional Review for ADHD and Neurocognitive Health: Foundations for the BRAIN diet.**2 " Paul Houston<sup>1</sup>, Larry Callahan<sup>2\*</sup>, Nina Fishcher-Yargici<sup>3</sup>, Alberto Paderno<sup>4</sup> · Nikhil Yadala<sup>5</sup> ,  
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20 Loose ends;

- 21 1. Histamine is not featured yet
- 
- 22 2. Need to add toxic metals under ANS dysregulation (lead etc)

23  
24 Word count 15930 + 6k of references total 22, 930 – 26th June25 **Keywords: ADHD, B.R.A.I.N diet, neurodevelopmental disorders, neurodegenerative  
26 diseases, inflammation keywords. (Min.5-Max. 8)**

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Confidential

95 **Abstract –**

96 For full guidelines please refer to [Author Guidelines](#)

97  
98 ADHD, bipolar disorder, schizophrenia, multiple sclerosis, and Alzheimer's disease  
99 may share overlapping biological dysfunctions, including chronic inflammation,  
100 neurochemical imbalance, and mitochondrial impairment. Pharmacological  
101 treatments can alleviate symptoms but rarely address these root causes and may  
102 contribute to further dysregulation. Poor diet is another modifiable driver of these  
103 interconnected pathways. Evidence shows that targeted dietary interventions,  
104 particularly those incorporating polyphenols, omega-3 fatty acids, pre- and  
105 probiotics, and key micronutrients, can improve ADHD symptoms, especially in  
106 individuals who do not tolerate or respond to medication. This paper gives a  
107 narrative review plus a conceptual synthesizes of the current research on ADHD-  
108 related biological systems dysregulation and dietary support presenting the  
109 scientific rationale for the B.R.A.I.N. Diet (Bio-Regulation Algorithm and Integrated

110 Neuronutrition), a precision, whole-food diet designed to optimize brain health  
111 through integrated nutritional strategies.

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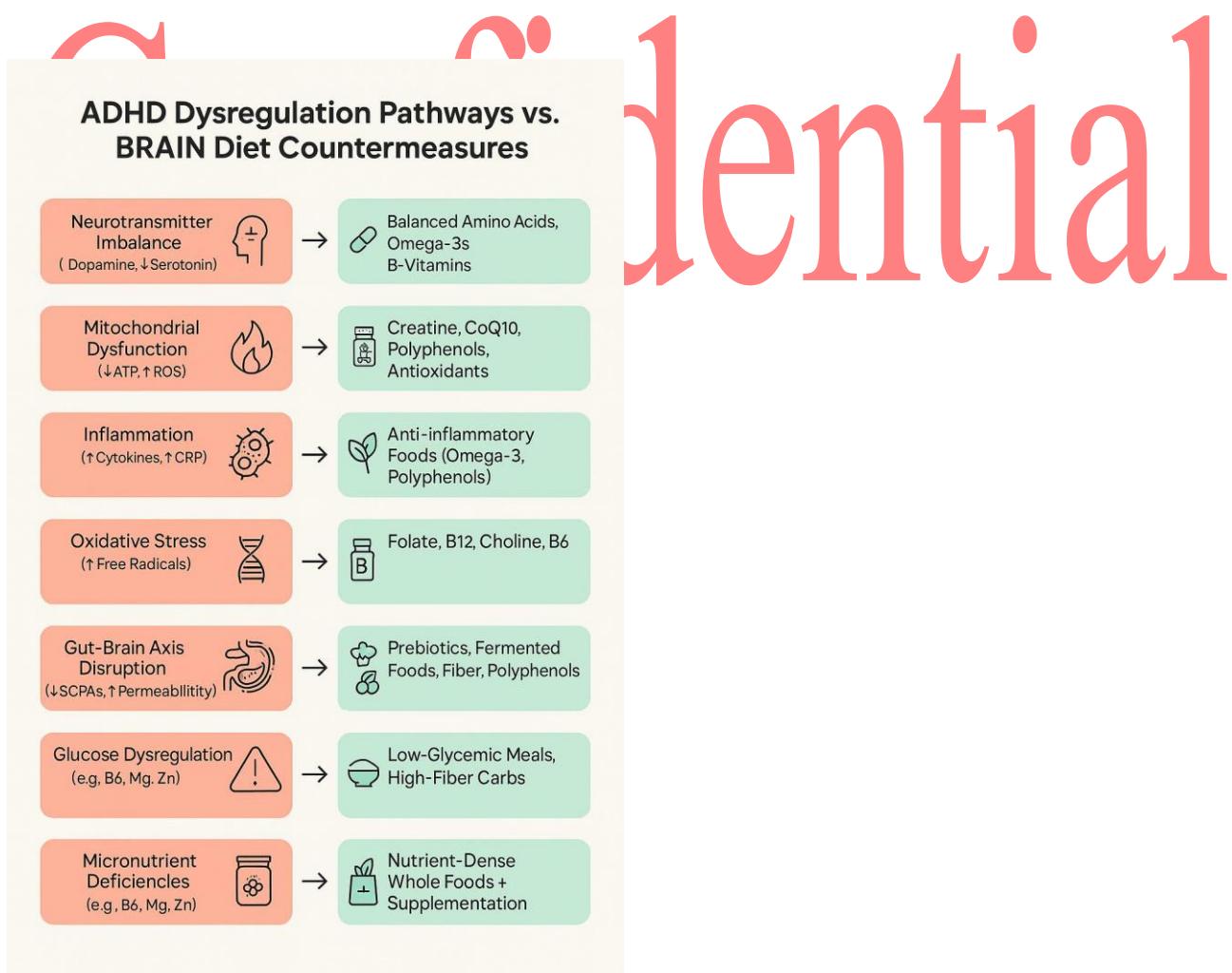
113 **1. Introduction**

114

115 ***Overview of key dietary foundations***

116 Neurodevelopmental disorders such as ADHD, ASD, and bipolar disorder, and neurodegenerative  
117 conditions like Alzheimer's and Parkinson's disease, have complex, multifactorial origins. Although  
118 the precise causes are not fully understood, these conditions share overlapping biological  
119 dysfunctions, including mitochondrial impairment, chronic inflammation, oxidative stress, impaired  
120 methylation, gut–brain axis disruption, glucose dysregulation, micronutrient deficiencies, and  
121 neurotransmitter imbalances (Figure 1). These interconnected systems, while not sole causes of such  
122 disorders, can contribute to symptom burden and overall metabolic and mental health.

123



124

125 Targeting these pathways through nutrition offers a low-risk approach with potential to improve  
126 brain health and, in some cases, alleviate ADHD symptoms by optimising overall neurobiological  
127 function. Dietary interventions have been shown to slow cognitive decline (Agarwal et al. 2023;  
128 Katonova et al. 2022) and may help stem progression from neurodevelopmental to  
129 neurodegenerative conditions ((Leffa et al. 2023; L. Zhang et al. 2022)).

130 An extensive literature review found no existing long term dietary protocol, that is both low-risk and  
131 comprehensive in applying a systems-based approach to improving brain health. Given the genetic  
132 overlap, shared biological mechanisms, and correlated symptom profiles among neurodevelopmental  
133 and neurodegenerative conditions, we propose that a targeted brain health diet may offer more  
134 potential in reducing the wide-ranging and often debilitating symptoms that individuals with these  
135 disorders experience. The focus of this paper is anchored in ADHD and brain health which supports  
136 ADHD but also it is hypothesized that individuals experiencing other brain related conditions like  
137 ASD, Bipolar, Alzheimer's etc would benefit.

### 138 ***Researched dietary interventions for ADHD***

139 The most widely trialled dietary strategies for ADHD, historically have been:

- 140 • **Restricted Elimination Diets (RED)**  
141 • **Artificial Food Colour Elimination (AFCE)**  
142 • **Omega-3 / Polyunsaturated Fatty Acids (PUFA) supplementation**  
143 • **Targeted vitamin–mineral combinations**

144 There have been several diets that focused on ADHD these include: Restricted Elimination Diets  
145 (RED) (Rommelse and Buitelaar 2013)(Rommelse and Buitelaar 2013), Artificial Food Color  
146 Elimination (AFCE), Omega-3 fatty acids or Polyunsaturated Fatty Acids (PUFA) supplementation,  
147 and also targeted vitamin and mineral combination studies. A meta-analyses(Stevenson et al. 2014)  
148 (Stevenson et al. 2014) found the range of average effect sizes in standard deviation units as follows:  
149 RED (0.29–1.2), AFCE (0.18–0.42) and PUFA (0.17–0.31).

150 The foundations of the Mediterranean diet ( high consumption of fruit, vegetables, legumes, olive oil,  
151 and moderate consumption of fish and white meat), are an excellent basis for improving overall  
152 health and these diets have shown some efficacy against a wide array of conditions like  
153 ADHD(Aksoy and Doguer 2025) (Darabi et al. 2022), Alzheimers (Morris et al. 2015) (Ashley  
154 Holub 2022), . Conversely studies have shown that an unhealthy western diet can trigger  
155 ADHD(Horner et al. 2025) (Howard et al. 2011).

### 156 ***Other diets with potential for ADHD – Keto and Fast Mimicking***

157 Given the rising rates of neurodevelopmental and neurodegenerative disorders, or at least the  
158 identification of them, the need for evidence based nutritional interventions to support cognitive  
159 function and mental health has never been more urgent. Recent dietary strategies such as the  
160 Ketogenic diet (Galali et al. 2024) and the Fast Mimicking Diet(Rangan et al. 2022) have contributed  
161 significantly to the field by demonstrating targeted metabolic and neurological benefits, while studies  
162 are still limited, and with mixed results larger more tightly controlled studies are needed (Omori et al.  
163 2024). However, concerns remain regarding the long-term safety and feasibility of such approaches,  
164 for example the ketogenic diet, is associated with warnings against long term health concerns such as  
165 cardiac risk, poor lipid profiles and possible glucose intolerance (Crosby et al. 2021; Popolek-Kalisz  
166 2024; Joo et al. 2023; W. Li et al. 2024). Consideration of inducing ketosis via plant fats may reduce

167 the health burden and prove equally effective(Fuehrlein et al. 2004).Meanwhile, the Fast Mimicking  
168 Diet is intended to be implemented upon five day cycles with the expectation that normal dietary  
169 habits resume after that period.

170 ***The B.R.A.I.N Diet Overview***

171 The BRAIN Diet (Bio-Regulation Algorithm and Integrated Neuronutrition); for neuronutrition see  
172 (Badaeva et al. 2023) is A Mediterranean-Rooted Precision Nutrition Model . It is a plant-based  
173 leaning protocol i.e. (70% minimum energy minimum from plants). The research highlights  
174 advantages and possible nutritional shortcomings of vegan diets and while trying to address as many  
175 of these gaps as possible with natural food solutions, research shows that vegans commonly take  
176 essential supplements.

177 While plants form the foundation with high polyphenol count targets and targeted herbs and spices,  
178 the omnivore version of the diet also incorporates nutrient-dense animal foods such as seafood, eggs,  
179 fermented dairy, occassional offal (Latouch et al. 2024) i.e. liver and lean animal proteins. There is a  
180 gut microbiome focus via a wide array of gut supporting nutrients and other key brain supporting  
181 nutrients such as omega 3, creatine, Coq10, etc.

182 The BRAIN Diet adheres to international nutritional intake guidelines while allowing  
183 for **personalisation based on other complementary individual goals besides brain health**, such as  
184 building muscle mass, gut healing, food sensitivities or intolerances, or aligning with ethical and  
185 environmental values.

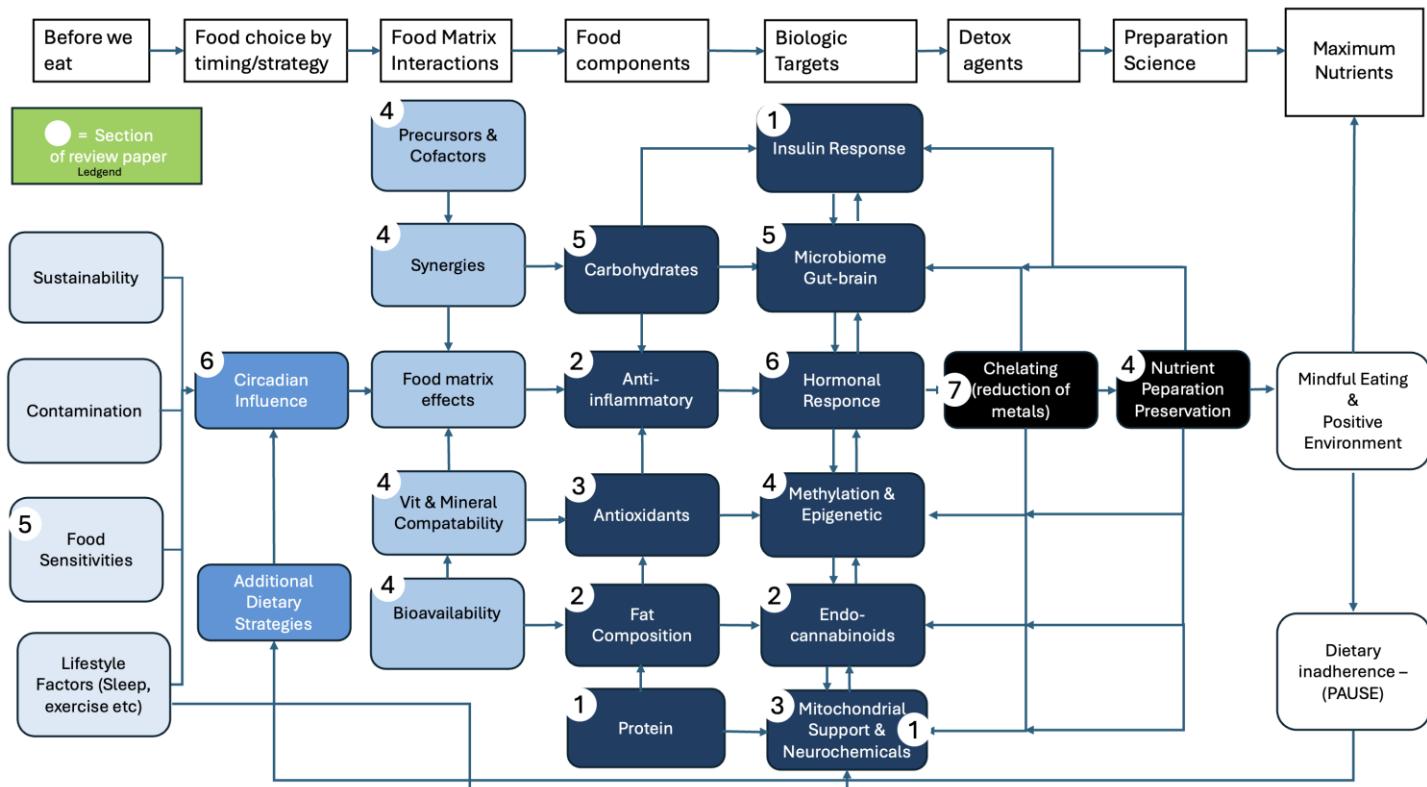
186 This is a **food-first, no-supplement baseline** approach designed to modulate key biological systems  
187 commonly disrupted in ADHD, depression, cognitive decline, and other neurocognitive disorders.  
188 Vegan participants may be more likely, as is currently the case to take supplements but the diet will  
189 target the widest array of food types to match the nutrient breadth and targets of the omnivore  
190 version, but all targets cannot be met from plants alone. While inspired by the Mediterranean diet's  
191 strengths in cardiometabolic health, the BRAIN Diet advances this model by incorporating:

- **Targeted micronutrient density** (e.g., magnesium, B6, choline, zinc, iron)
- **Neurotransmitter precursor support** (e.g., tyrosine, tryptophan, choline, DHA)
- **Circadian-aligned meal timing**, especially **protein-rich breakfasts**
- **Food matrix strategies** to improve nutrient synergy and bioavailability
- **Psychobiotic and polyphenol-rich foods** for gut-brain axis regulation
- **Mitochondrial support and methylation pathway modulation**

198

199 The Framework which supports the BRAIN diet is depicted below (Figure 2). This paper focuses  
200 primarily on the research relating to the subjects under the “Food Matrix”, “Food Components”  
201 “Biological Targets” and “Preparation Science”. However, the sourcing, the ethics and the mindful  
202 eating strategies as represented in the framework are all essential elements that would contribute  
203 towards treating food as a legitimate, medical-grade intervention.

204



205

206 Figure 2 – Overview of BRAIN dietary framework.

207 Many of the biological mechanisms discussed below, such as gut microbiome composition, gut-brain  
 208 axis dynamics, and neurotransmitter regulation, are still emerging fields. They require further  
 209 exploration through larger, more nuanced human studies to strengthen their clinical relevance, but  
 210 some positive human studies exist and much preclinical research indicates dietary interventions could  
 211 be highly beneficial.

## 212 2. Food Matrix Interactions

213 The ‘food matrix’ is the integrated physical and chemical environment in which nutrients and  
 214 bioactives exist, influencing digestion, absorption, and biological effect. This perspective moves  
 215 beyond reductionist nutrient counting to a systems-based view of whole foods, preparation methods,  
 216 and synergistic pairings. (Fardet and Rock 2015). It factors in the complex physical and chemical  
 217 environment in which nutrients and bioactives exist including knowledge of the interaction of foods,  
 218 particularly whole foods, as part of a meal, and those synergies and interactions which are introduced  
 219 when eating foods together.

220 The food matrix also factors in how the body processes those nutrients, including:

221

- 222 • Bioaccessibility (Auer et al. 2024)(Auer et al. 2024) (what's released during digestion) ; will  
 223 depend on antinutrients, cell wall structure(Holland et al. 2020), preparation method i.e.  
 224 sprouting, soaking, manufacturing i.e. roasting, cleaving etc(Opazo-Navarrete et al. 2025)  
 225 (Opazo-Navarrete et al. 2025).
- 226 • Bioavailability (what's actually absorbed into the bloodstream).

- 227 • Biotransformation by the gut microbiome i.e. studies have shown Urolithin A, a antioxidant  
228 isn't absorbed the same by everybody(Singh et al. 2022) (Singh et al. 2022) , those with  
229 increased gut biota Firmicutes-to-Bacteroidetes ratio were more successfull .

230 This body of knowledge also includes the science of food preparation and cooking, and the resulting  
231 biologic interactions and metabolic outcomes. A milestone study by (Haber et al. 1977) demonstrated  
232 how apple juice compared to apple puree or a ‘whole food’ and how the juice caused a much greater  
233 insulin spike while also resulting in reduced satiety.

### 234 **The State of Bioavailability Information**

235 In nutritional therapy it is essential to maximise nutrient bioavailability through strategic food  
236 combinations, particularly for individuals with ADHD, where micronutrient status often plays a role  
237 in symptom modulation. While complete food matrix interactions and synergistic bioavailability  
238 effects remain largely un-mapped (Melse-Boonstra 2020) existing literature provides key  
239 foundational estimates from which real nutritional advantages can be gained (Gibson 2007). While  
240 food labeling systems may not yet account for these variables, emerging nutritional science offers  
241 enough insight to strategically design diets that harness matrix effects for improved metabolic and  
242 cognitive outcomes.

### 243 ***The need to make knowledge open and accessible***

244 A wealth of nutritional science lies in the publications of food scientists such as Harold McGee,  
245 Heston Blumenthal, and Nathan Myhrvold and other pioneers who have brought deep biochemical  
246 understanding to the culinary world. However the majority of food science principles remain locked  
247 away in firewalled scientific journals, representing a hugely wasteful opportunity to improve public  
248 health. However open-access nutritional and bio-chemistry journals do provide a rich source of  
249 knowledge we highlight some key studies below.

### 250 ***Food Preparation in managing harmful and healthful byproducts***

251 Knowledge driven preparation of food is essential in creating clinical grade meals where nutrients  
252 are preserved, including antioxidants, and antinutrients are reduced (phytates, lectins, oxalates,  
253 tannins) and harmful food byproducts i.e. those created through excessive heat and oxidation.

### 254 **Oxidation End Products**

255 Oxidation end products are reactive compounds formed when fats, proteins, and carbohydrates  
256 undergo heat- or oxidation-driven chemical changes during cooking and storage; their accumulation  
257 can disrupt cellular function and has been linked to metabolic, cardiovascular, and neurodegenerative  
258 disorders. There are also a set of antinutrients which can be strategically reduced via preparation  
259 methods, we outline some of the key examples below.

260 One of the most well known, particularly by chefs, is the malliard reaction. This is the surface  
261 browning seen on food when heated sugars oxidise with amino acids, it can be used as a visual  
262 mechanic to steer food away from a damaging level of cooking. The malliard properties ( or  
263 Maillard reaction products (MRPs) of some foods actually have antioxidant properties though this is  
264 more common in carbohydrate high foods, breads etc, not so much in meats, unless sugar containing  
265 marinades are used.

266 MRPs possess excellent antioxidant ability in many food products, through chelation of metal ions,  
267 breakdown of radical chains and hydrogen peroxide, and scavenging of reactive oxygen  
268 species(Nooshkam, Varidi, and Bashash 2019). There is a point which needs to be avoided through  
269 precise cooking so antioxidants don't break down and harmful byproducts don't appear such as  
270 acrylamide and HCAs and PAHs(Edna Hee et al. 2024).

271 **Antinutrients**

272 In the context of a diverse, well-prepared diet, **antinutrients such as phytates, oxalates, lectins,**  
273 **and tannins** rarely pose a threat to nutrient status or cognitive health. In fact, many of these  
274 compounds have **dual roles**, with emerging evidence pointing to **health-protective properties** such  
275 as antioxidant and anti-inflammatory effects.

276 Unless a person has specific risk factors (e.g. mineral deficiency, kidney stones, gut permeability),  
277 there's little evidence that dietary antinutrients cause harm. While phytates can bind essential  
278 minerals such as zinc, iron, and calcium, potentially impairing their absorption, they can also exhibit  
279 antioxidant properties, and have been associated with reduced risk of kidney stones and some cancers  
280 (Taylor et al. 2009).

281

Topic	Brain Health Relevance	Key References
Maillard Reaction Products (MRPs)	Controlled Maillard browning in whole grains can yield antioxidant melanoidins; excessive browning generates acrylamide, heterocyclic amine (HCAs), and polycyclic aromatic hydrocarbons (PAHs) which are neurotoxic.	(Nooshkam et al. 2019)(Coda et al. 2010)
Advanced Glycation & Lipoxidation End Products (AGEs / ALEs)	High-heat cooking of fats and proteins produces AGEs/ALEs, which can cross the BBB, activate microglia, and impair synaptic plasticity—mechanisms implicated in cognitive decline.	(Uribarri et al. 2010)
Soaking & Sprouting Strategies	Reduces phytates in legumes/grains, improving non-heme iron and zinc bioavailability; germination can increase GABA and antioxidant content, supporting neurotransmitter balance.	(GREINER and KONIETZNY 1999)
Reducing Dietary Oxalates	Boiling spinach, kale, and other greens can reduce oxalate load, improving mineral bioavailability; excess oxalate may disrupt mitochondrial function and redox status.	(W. Chai and Liebman 2005)

282 **Table X** food matrix-related preparation strategies

283 Detailed protocols, extended literature reviews, and mechanistic diagrams are  
284 provided in *Supplementary Appendix 1*.

285 **3. Micronutrients and Nutrient-Dense Foods for Brain Health**

286  
287

288 Micronutrients not only drive enzymatic pathways directly, but also act as gatekeepers for other  
289 dietary bioactives. Their availability can determine whether compounds such as omega-3 fatty acids,  
290 polyphenols, or amino acid precursors exert their intended effects. This interdependence highlights  
291 the importance of viewing nutrition as a network rather than in isolation.

292  
293 Vitamins and minerals function as indispensable micronutrients and enzymatic cofactors  
294 in pivotal brain biology pathways, aiding neurotransmitter synthesis, mitochondrial energy  
295 production, DNA repair, antioxidant defense, methylation, and the regulation of neuroplasticity  
296 (Tardy et al. 2020) with B-vitamins playing a central role (Kennedy 2016).  
297 For a wide array of vitamins and minerals research suggests that increased adherence to the  
298 Mediterranean diet is effective in targeting essential vitamins and minerals, due to the wide array of  
299 fruits, vegetables, and healthy fats (Castro-Quezada, Román-Viñas, and Serra-Majem 2014).

300  
301  
302 **Recommended Daily Amounts and Revisions**  
303

304 There are many shifts in the considerations of the RDAs and recent research has highlighted  
305 potential shortfalls in long considered optimal RDAs such as vitamin D, b6, and b12.. Many studies  
306 have hypothesized that many vitamins can have more benefits when dosed well above RDAs and  
307 more towards upper tolerable limits, particularly water soluble vitamins such as B vitamins (Kennedy  
308 2016)(Kennedy 2016) which are not stored in the body in any significant amount with excesses being  
309 quickly excreted through urine. The brain however has more careful longer term control over  
310 nutrients so shortfalls are not experienced so frequently

311  
312 Recent studies however have noted a lack of Pharmacokinetic data available to inform any real  
313 dietary precision in interim daily dosing of vitamins (Sugandhi et al. 2024).  
314 Water soluble vitamins B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6  
315 (pyridoxine), B8 (biotin), B9 (folic acid), B12 (cobalamin), and vitamin C (ascorbic acid) must be  
316 regularly included in the diet to prevent deficiency

317

318 **Micronutrient Supplementation for ADHD**

319

320 Research indicates that deficiencies in vitamins and minerals essential for methylation, such as folate,  
321 vitamin B12, and zinc, are correlated to ADHD symptoms and that supplementing these  
322 micronutrients has shown potential in supporting methylation and reducing symptom severity  
323 (Razavinia et al. 2024) . Other common deficiencies, particularly linked with children, are iodine and  
324 iron (“WHO Micronutrient Deficiencies” 2025). A large Australian cohort study, discussed in the  
325 review by (Millichap and Yee 2012) found that dietary patterns rich in fiber, folate, and omega-3 fatty  
326 acids were associated with reduced ADHD symptoms.  
327

## 328 ***Nutrient Density***

329 As we've seen throughout this paper, the full power of nutrient-network effects depends on the  
330 consistent availability of key dietary precursors and synergistic nutrients. Whether it's supporting a  
331 diverse gut microbiome, network polyphenol interactions, a broad spectrum of vitamins and  
332 minerals, optimal amino acid profiles from plant and/or animal sources, or balanced omega-3 to  
333 omega-6 ratios, all of these inter-related nutrients can only work when highly nutritional food targets  
334 that provide these cofactors and precursors are regularly provided. While it's not realistic to meet  
335 every nutritional need every single day, nutrient-dense foods give us the best opportunity to build  
336 meals that support these complex physiological demands, so that over time, most recommended daily  
337 requirements are met.

338 This goes beyond a standard nutrient density focus, it's about choosing foods for their specific  
339 bioactive potential: extra virgin olive oil with higher levels of CoQ10 and polyphenols, grass-fed  
340 liver for bioavailable retinol and B12, mucuna beans for natural L-DOPA(Gasmi et al. 2022),  
341 traditionally fermented breads that optimize Maillard Reaction Products (MRPs), or cooled grains ,  
342 fish roe for phospholypic bound omega 3 or algal oil for vegetarians etc . Even the water we drink,  
343 ideally filtered and re-mineralized and occasional red wine, should be selected by its tannin and  
344 antioxidant profile.

345  
346

347 **Cobalamin (B12):** is crucial role in its involvement in the conversion of methylmalonyl-CoA to  
348 succinyl-CoA , a key step in mitochondrial energy production. A deficiency in B12 can lead to a  
349 buildup of methylmalonic acid and odd-chain fatty acids, which are neurotoxic and contribute to  
350 myelin sheath damage. This disruption is linked to symptoms such as memory loss, brain fog,  
351 depression, and even early signs of dementia, vitamin B12 deficiency may even lead to dementia and  
352 psychosis, suggesting a broader dependence of the brain on B12, it is also commonly deficient in  
353 vegetarians (Pawlak et al. 2013).

354

- 355     ● **Thiamine (B1):** Critical for pyruvate dehydrogenase (PDH) and mitochondrial α-KGDH,  
356       thiamine supports aerobic metabolism. Deficiency leads to impaired pyruvate entry into the  
357       TCA cycle, causing lactate buildup and metabolic dysfunction, which is associated with  
358       cognitive impairments in ADHD.
  - 359         ○ Absorption Rate: About 50–90% from dietary sources; absorption can decrease if  
360           consumed in very high doses or with alcohol, which can impair thiamine uptake.
  - 361         ○ RDA: 1.2 mg for men, 1.1 mg for women.

- 362                   ○ Supplement Note: Supplementation (50–100 mg) may support those with neurological  
363                   issues, chronic stress, or fatigue. High doses are sometimes used to support brain  
364                   health or in cases of thiamine deficiency.(Doshi et al, n.d.; Pawlak et al. 2013)

- 365                   ● **B3 - Niacin (B3):** Crucial for NAD<sup>+</sup> and NADP<sup>+</sup>, niacin is involved in glycolysis and the TCA  
366                   cycle. Lack of niacin hampers NAD<sup>+</sup> regeneration, decreasing ATP production and  
367                   potentially affecting cognitive performance (Pirinen et al. 2020).

- 368  
369                   ● **Pantothenic acid (B5):** Essential for CoA and PDH function, which are necessary for TCA  
370                   cycle energy generation. Deficiency impairs fatty acid oxidation and ATP production,  
371                   potentially affecting brain energy levels (Liu et al., 2017).

- 372                   ○ **Absorption Rate:** 50–80% from dietary sources, mostly absorbed as CoA.  
373                   ○ **RDA:** 5 mg for adults.  
374                   ○ **Supplement Note:** Supplementation isn't typically necessary but may be useful in  
375                   high-stress situations, as pantothenic acid supports adrenal function. Common  
376                   supplemental doses range from 100 to 1,000 mg.

377                   ● **B6 'Pyridoxine' active form P5P pyridoxal-5'-phosphate**

- 378                   ○ In ADHD, genetic variations and enzymatic inefficiencies can influence metabolic  
379                   pathways critical for neurotransmitter synthesis, including the activation and  
380                   utilization of vitamin B6. Pyridoxine kinase (PDXK) is one such enzyme essential for  
381                   converting dietary vitamin B6 (in the forms of pyridoxine, pyridoxal, and  
382                   pyridoxamine) into pyridoxal-5'-phosphate (P5P), the bioactive form. Deficiencies or  
383                   inefficiencies in this conversion may impact key processes involved in ADHD  
384                   symptoms. B6 and magnesium are cofactors and doses of b6 and magnesium have  
385                   been found to reduce inattention and hyperactivity (M Mousain-Bosc 1 2006). b6 is  
386                   not highly bioavailable in plant based diets and vegan populations can be deficient ,  
387                   particularly older individuals (Waldmann et al. 2006).

- 388                   ● **Iron and Ferritin:** The relation to iron and ADHD is complex and iron supplementation has  
389                   not proven effective in relieving ADHD symptoms possibly because iron also catalyzes  
390                   reactions that increase oxidative stress. Iron has to be considered in it's relationship with  
391                   Ferritin. Ferritin, an intracellular protein, stores iron and regulates its release, thereby limiting  
392                   the amount of free iron that can produce oxidative radicals . In ADHD patients, lower serum  
393                   ferritin levels were however found compared to controls. This implies a lower regulation of  
394                   iron, resulting in more free iron and thereby potentially creating more oxidative stress,  
395                   ○ **Iron Absorption Rate:** Highly variable (14–18% from supplements).  
396                   ○ **RDA:** 8 mg for men, 18 mg for women.  
397                   ○ **Supplement Need:** Many iron supplements provide more than the RDA to  
398                   compensate for low absorption rates.

- 399                   ● **Vitamin D:** Vitamin D is crucial for brain development and cognitive function. It regulates  
400                   neurotrophic factors, which are vital for the survival and growth of neurons, and modulates  
401                   immune responses to reduce inflammation in the brain. It is highly prevalent for populations to  
402                   have high levels of vitamin D deficiency and this is particularly important for those  
403                   consuming vegetarian and vegan diets, where there is a low intake of animal-based  
404                   vitamin D. One study looked at the modelling in dietary guidelines with a view to  
405                   expediting the global acceptance of UV-exposed mushrooms as a source of vitamin  
406                   D.(Starck et al. 2024)**Absorption Rate:** Fat-soluble, best absorbed with food containing fat.

- 407           ○ **RDA:** 600–800 IU.  
408           ○ **Supplement Need:** Many people take 1,000–2,000 IU to ensure adequate blood  
409           levels, especially in low-sunlight environments.
- 410           ● **Magnesium** supports neurotransmitter regulation, especially GABA (an inhibitory  
411           neurotransmitter). Deficiency is common in those with ADHD and can exacerbate  
412           symptoms like irritability and attention difficulties. Supplementation with other  
413           compounds such as vitamin D have shown to significantly reduce behavioural  
414           problems be effective (Hemamy et al. 2020). Other studies have shown magnesium to  
415           be effective with both zinc and omega 3 and 6(Huss, Völp, and Stauss-Grabo 2010).
- 416           ○ Magnesium is involved in over 300 enzymatic reactions, including:  
417              ■ modulating glutamate receptors  
418              ■ magnesium binds to ATP and all triphosphates in a cell to activate it  
419              ■ its as a cofactor in enzymes of glycolysis and the Krebs cycle ( the processes  
420              that generate ATP from glucose )  
421              ■ it assists enzymes involved in the synthesis of dopamine and serotonin  
422              ■ it also helps manage stress responses.  
423              ■ Key mechanism in fighting pro-oxidants and supporting antioxidants(Zheltova  
424              et al. 2016)  
425           ○ **Absorption Rate:** 30–40%.  
426           ○ **RDA:** 310–420 mg.  
427           ○ **Supplement Need:** Often taken in amounts close to or above the RDA (200–400 mg)  
428           due to limited absorption from foods.
- 429           ● **Manganese** Manganese is a cofactor for mitochondrial superoxide dismutase (SOD2) the  
430           primary antioxidant enzyme within mitochondria. It is also linked to mild cognitive decline  
431           and Alzhiermers. (Du et al. 2017).  
432              ○ **Manganese absorption** occurs in the small intestine, where it competes with **calcium**  
433              , **iron** , **magnesium**, and **zinc**.
- 434           ● **Zinc:** Zinc is important for DNA synthesis, cell division, and neurotransmitter regulation,  
435           particularly in modulating dopamine—a key neurotransmitter implicated in ADHD.Higher  
436           doses are sometimes recommended (e.g., 15–30 mg), especially in those with absorption  
437           issues. Studies have shown benefits from higher doses of 30 mg in increasing BDNF(Agh et  
438           al. 2022).
- 439           ● **Iodine** is essential for the synthesis of thyroid hormones (T3 and T4), which are crucial for  
440           brain development and maturation. Thyroid hormones influenced by iodine are involved in  
441           the synthesis and regulation of key neurotransmitters like dopamine and serotonin  
442              ○ RDA 150 mcg/day
- 443           ● CoQ10 -

444  
445  
446         The dietary algorithm needs to consider the storage and complementary and sometimes competing  
447         mechanisms of all vitamins and minerals where available. Improved efficacy of spreading vitamins  
448         through the day i.e. as b.i.d. dosing was found to be more effective for zinc glycinate(Arnold et al.  
449         2011),(Akhondzadeh, Mohammadi, and Khademi 2004). To optimize those micronutrients critical to

450 health a balanced and broad diet is essential but also nutritionally rich foods which include high  
451 levels of nutrients.

452

453

454 ***Closing the Vegan Nutrient Target Gaps***

455 While the BRAIN Diet emphasizes food synergy and systems biology over isolated supplementation,  
456 vegan versions of the protocol must still address key nutrient gaps that are difficult to close through  
457 whole foods alone. These include vitamin B12, DHA/EPA, choline, taurine, carnosine, creatine, and  
458 bioavailable iron and zinc, nutrients typically abundant in animal products. Precision sourcing of  
459 functional plant-based ingredients such as **Mankai duckweed** (for B12 and iron), **algal oil** (for  
460 DHA), **fermented soy** (for choline), and **fortified nutritional yeast** (for B12 and B6) allows for  
461 meaningful progress. Inclusion of **spirulina** or **chlorella**, though limited by inactive analogues in the  
462 case of B12, may still offer adjunctive benefit for amino acid profiles and antioxidant capacity. In  
463 cases where whole-food intake cannot achieve therapeutic levels, strategic supplementation (e.g.,  
464 methylcobalamin, creatine monohydrate, or liposomal iron) may be required to maintain  
465 neurochemical and metabolic balance.

466

467

468 **4. Protein & Amino Acid Sources – ‘Neuronutrition Core’**

469 While micronutrients set the enzymatic processes driving brain health, it is the careful balance of the  
470 macronutrients, protein, fats, and carbohydrates, that must work in harmony with our circadian  
471 rhythms. Together, they regulate the key biological systems that shape everything from brain energy  
472 and inflammation to cognition and mood.

473 Protein, one of the three primary macronutrients alongside fats and carbohydrates, is perhaps the  
474 most debated area of nutrition. Its nuances span quality, source, frequency, digestibility, and  
475 recommended intakes, all of which vary depending on the goal, be it longevity, muscle retention,  
476 metabolic health, or, in the case of this paper, brain health.

477 The BRAIN Diet must account for these variables while ensuring that nutrition meets brain-specific  
478 nutrient targets. This includes recognising that several brain-relevant nutrients are predominantly or  
479 exclusively found in animal-sourced proteins—such as creatine, taurine, Coenzyme Q10 (also in  
480 smaller amounts in olive oil; (Zmitek, Rodríguez-Aguilera, and Pravst 2014)), and vitamin B<sub>12</sub> (also  
481 present in Wolffia globosa; (Kaplan et al. 2019)). Achieving the right balance between plant and  
482 animal proteins is therefore essential, both for nutritional adequacy and for ensuring the diet remains  
483 sustainable, inclusive, and neurologically effective over the long term.

484 Protein requirements are context-dependent: age, activity level, health goals, and personal values all  
485 influence optimal intake. While general recommendations sit at around 0.83 g/kg/day (“Scientific  
486 Opinion on Dietary Reference Values for Protein,” 2012), a meta-analysis (Morton et al., 2018)  
487 showed that intakes up to 1.62 g/kg/day can maximise gains in fat-free mass during resistance  
488 training, with no additional benefit beyond that point. More recent work ((Trommelen et al. 2023))

489 indicates that protein consumed in larger boluses can maintain positive whole-body protein balance  
490 over several hours, suggesting some flexibility in distribution.

491 Achieving the right balance between plant and animal protein sources is essential not only for  
492 nutritional adequacy, but also for ensuring that the BRAIN Diet remains sustainable, inclusive, and  
493 neurologically effective over the long term.

494

495 ***Balancing animal and plants for brain health***

496 While observational studies frequently link vegetarianism with reduced chronic disease risk, the  
497 relationship between diet type and brain health is more nuanced. Significant research gaps remain,  
498 but existing research indicates truly optimal brain-focused nutrition may require a more strategic  
499 approach that combines plant-based diversity with targeted animal-derived nutrients.

500 A recent Taiwanese cohort (J.-H. Tsai et al. 2022)) of 5,710 adults found that vegetarians had a 33%  
501 lower risk of dementia compared to non-vegetarians. Similarly, Mediterranean dietary patterns have  
502 shown neuroprotective effects, reducing dementia risk between 22–33% ((Shannon et al. 2023)),  
503 even after correcting for genetic risk. Epidemiological data do not indicate that excluding all animal  
504 foods is necessary for longevity, but rather that plant-forward diets, such as the Mediterranean, often  
505 include modest amounts of dairy, fish, and meat, which are common denominators in Blue Zones  
506 (Buettner and Skemp 2016).

507 Conversely, several studies highlight nutrient shortfalls in fully plant-based diets that may undermine  
508 cognitive resilience. (Katonova et al. 2022)) note that while vegan diets are low in saturated fats and  
509 cholesterol and rich in antioxidants and fiber, they can lack vitamin B12, vitamin D, DHA, and  
510 certain minerals, all of which are critical for brain health. Supporting this concern, (Jigeer et al.  
511 2025) found that vegetarians in their 80s had higher odds of cognitive impairment compared to  
512 omnivores, likely due to deficiencies in B12, EPA/DHA, and zinc.

513 Evidence also suggests that some degree of seafood intake may be necessary for optimal cognitive  
514 outcomes. In a two-year follow-up of Dutch older adults, (van Soest et al. 2023) found that adherence  
515 to a healthful plant-based diet did not improve cognition or slow decline unless participants  
516 consumed at least one weekly portion of fish. This aligns with MIND diet research, where high  
517 polyphenol intake (leafy greens, berries) combined with key animal-derived nutrients produced  
518 measurable neuroprotective effects (. (van den Brink et al. 2019; Agarwal et al. 2023).).

519 The BRAIN Diet is designed to capture these dual benefits, leveraging abundant plant foods for  
520 antioxidants, polyphenols, and fiber, while strategically including animal-derived sources of CoQ10,  
521 creatine, taurine, and omega-3 fatty acids. For omnivores, this means leaning toward a predominantly  
522 plant-based pattern with purposeful selection of animal proteins. For plant-based eaters, it involves  
523 optimising brain health through a wide variety of nutrient-dense foods and supplementing where  
524 dietary gaps are hard to fill.

525 **Table X** (below) compares the contribution of key brain-health nutrients which are normally  
526 predominantly available from animal sources, highlighting why the BRAIN Diet incorporates both  
527 plant-forward diversity and targeted inclusion of animal proteins or equivalent supplementation.

528

Nutrient	Primary Role in Brain Health	Top Animal Sources (DIAAS ≥100 where possible)	Top Plant / Vegan Sources	Notes on Deficiency Risk in Vegan Diets
Creatine	Supports ATP recycling in neurons; enhances working memory and cognitive processing speed	Beef, lamb, pork, salmon, tuna, cod, scallops	Minimal — trace amounts in seaweed (e.g., nori)	Vegan diets lack creatine; supplementation or fortified foods may be needed
Coenzyme Q10 (CoQ10)	Mitochondrial electron transport; antioxidant protection for neurons	Organ meats (heart, liver), oily fish (sardines, mackerel), beef	Spinach, broccoli, pistachios, olive oil (lower amounts)	Plant forms (ubiquinone) less concentrated; deficiency risk higher with age
Taurine	Regulates calcium signalling, antioxidant defence, and neurotransmission	Scallops, clams, dark-meat poultry, mackerel	Minimal in plants; trace in seaweed/algae	Deficiency risk for vegans; brain taurine levels tied to neuroprotection
EPA & DHA (Omega-3)	Anti-inflammatory; membrane fluidity; neurotransmitter receptor function	Sardines, mackerel, salmon, tuna, cod liver	Algal oil (direct DHA), seaweed (low bioavailable DHA/EPA)	Conversion from ALA is <5% in most adults; direct DHA/EPA strongly recommended
Vitamin B12	Myelin synthesis, methylation, neurotransmitter production	Liver, clams, fish, eggs, dairy	Fortified plant milks, nutritional yeast, supplements	Deficiency causes cognitive decline, mood disorders, neuropathy
Carnosine	Antioxidant, pH buffer, protects neurons from glycation and oxidative damage	Beef, pork, chicken	None	Absent in vegan diets; synthesised from histidine + beta-alanine, but beta-alanine mostly from animal food
Zinc	Neurotransmitter modulation, synaptic plasticity, antioxidant enzymes	Oysters, beef, crab, chicken, pork	Pumpkin seeds, lentils, chickpeas, cashews	Plant zinc less bioavailable due to phytates; soaking/sprouting helps
Iron(heme & non-heme)	Oxygen delivery to brain, dopamine synthesis	Liver, beef, lamb, poultry, fish	Lentils, spinach, tofu, pumpkin seeds	Heme iron from animal sources is 2–3× more bioavailable
Choline	Precursor to acetylcholine; supports memory and mood	Eggs, beef liver, chicken, fish	Soy lecithin, quinoa, broccoli	Choline needs higher in pregnancy and older age for cognition
Iodine	Thyroid hormone synthesis; regulates neurodevelopment	Seaweed, cod, dairy, eggs	Iodised salt, seaweed	Seaweed iodine content highly variable; risk of excess/deficiency

530  
531 Table X - key brain-health nutrients which are normally predominantly available from animal sources

532

533 ***Animal and Plant Based Protein Balance examples***

534 While most animal proteins provide all nine essential amino acids in optimal ratios, plant proteins  
535 require strategic pairing. (Mariotti and Gardner 2019)(figure 1.1 below) Many plants are often low in  
536 methionine and lysine so combinations such as grains or pseudograins with legumes can be essential  
537 for vegetarians. When key brain health dietary targets cannot be met through whole foods alone, the  
538 nutritional gaps could be made via appropriate supplementation. This is especially relevant for  
539 individuals following vegetarian diets, where key brain nutrients (table X above) are often found in  
540 lower amounts or are absent altogether.

541

542 ***Neurochemical Overview***

543 Neurochemicals are molecules that are responsible for communication between nerve cells, and nerve  
544 cells and other cells. They are typically classified based on their function which can be excitatory,  
545 inhibitory or modulatory in nature, although some neurochemicals can have multiple functions.  
546 Neurotransmitters can also be classified chemically as either amino acids, monoamines, purines, etc.

547

548 ***Neurotransmitter imbalances and Dopamine's wider implications***

549 Many neurological disorders are thought to be due to neurochemical imbalances although conclusive  
550 proof is often lacking. (Akyuz et al. 2025) and much research has now implicated much broader  
551 neurotransmitter dysregulation. A meta study analysis (MacDonald et al. 2024) concluded that while  
552 dopaminergic dysfunction is consistently linked to ADHD, evidence does not support a simple global  
553 hypo-dopaminergic model and that dopamine alterations vary by ADHD subtypes, developmental  
554 stage, and brain region, interacting with other neurotransmitter systems. (Perreault et al. 2014) noted  
555 the difficulties in really ‘disentangling’ pure dopaminergic neurotransmission from other transmitter  
556 systems; >200 chemical messengers (classical transmitters, neuropeptides, purines, lipid mediators,  
557 gases) have been described, underscoring the system’s complexity(Gasmi et al. 2022). This is why  
558 the BRAIN Diet must target broad neurochemical precursors and cofactors to support efficient  
559 neurotransmitter production.

560 Many neurological disorders are associated with neurochemical imbalances, although direct causal  
561 proof is often limited (Akyuz et al., 2025). Increasingly, evidence points toward *broader*  
562 *neurotransmitter dysregulation* rather than single-system deficits. A meta-analysis by MacDonald et  
563 al. (2024) concluded that while dopaminergic dysfunction is consistently linked to ADHD, the data  
564 do not support a simple global hypo-dopaminergic model. Instead, dopamine alterations vary by  
565 ADHD subtype, developmental stage, and brain region, and frequently interact with other  
566 neurotransmitter systems. As Perreault et al. (2014) note, disentangling “pure” dopaminergic  
567 signalling from the influence of other transmitters remains a significant challenge.

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568 For these reasons, the diet must target a *broad spectrum* of neurochemical precursors, while also  
569 integrating anti-inflammatory nutrients and gut-brain modulators i.e. to support balanced  
570 neurotransmitter production across systems—not dopamine alone. This approach aligns with dietary  
571 intervention research showing that nutrient patterns rich in amino acid precursors, omega-3 fatty  
572 acids, and polyphenols can influence dopamine, serotonin, GABA, and acetylcholine pathways  
573 simultaneously, supporting mood stability, attention, and cognitive performance.

574 **Default Mode Network (DMN).**

575  
576 Dopamine affects ADHD both as a crucial neurotransmitter involved in regulating attention, and  
577 executive functions and also as a neuromodulator affecting broader neural networks such as the  
578 Default Mode Network (DMN). The DMN are regions of the brain that are active during non-focused  
579 activity such as daydreaming. The inability to move from a DMN state to an executive state has been  
580 hypothesized as one of the causes of ADHD. Dopamine dysregulation in ADHD impairs the brain's  
581 ability to shift from rest-state (DMN) to focus-state networks. The BRAIN Diet uses nutrient-timed  
582 meals to support this transition through dopamine precursors and anti-inflammatory nutrients to  
583 reduce DMN dysregulation(Marsland et al. 2017). A meta-analysis has also shown that  
584 amphetamine based medications consistently (11 of 12 studies) restored connectivity in DMN  
585 areas(Santos et al. 2019).

586  
587 Individuals targeting dopamine via fatty and sugary foods is common in ADHD populations which is  
588 probably correlated to the double dopamine reward(Thanarajah et al. 2019) experienced when eating  
589 food. These orosensory and post-ingestion dopamine circuits and reward systems can be utilised as  
590 dietary strategies (Table 3 below),, they must be used sparingly as we discuss below eating is the  
591 best strategy when the body needs nutrition, at other times other interventions are available such as  
592 exercise or meditation.

593  
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Strategy	Rationale	Application in BRAIN Diet
<b>Use sensory-rich, but nutrient-dense meals</b>	Stimulate first dopamine release <i>without junk food</i>	Visual appeal, aroma, textures (e.g. colorful smoothie bowls, herbed protein dishes)
<b>Ensure real nutrient delivery for the second peak</b>	Reinforce positive reward loop through actual nutrition	Meals rich in tyrosine, omega-3s, magnesium, slow carbs
<b>Time meals to align with cognitive demands</b>	Harness reward-motivation boost around task performance	Morning and midday meals structured for work/school focus
<b>Build habit loops around consistent foods</b>	Condition dopamine response to healthy eating routines	Repeat satisfying meals at predictable times for brain entrainment
<b>Avoid ultra-processed foods</b>	These hijack the double dopamine system and lead to dysregulation and addictive behaviours(LaFata et al. 2024)	Emphasize whole foods and minimize synthetic flavors/sweeteners

597

598 Table 3. – Dopamine reward dietary strategies

599

600

601 **Glutamate** is the principal excitatory neurotransmitter of the central nervous system and the most  
602 abundant neurotransmitter in the brain. It has wide clinical relevance in neurology and psychiatry,  
603 specifically regarding depression, substance use disorder, schizophrenia, neurodegenerative diseases,  
604 and other cognitive function and mood deficits. (Zhou and Danbolt 2014). Low levels of glutamate  
605 in a number of critical brain areas correlated with low scores on the Barkley attention scale.  
606 .Maltezos et al. 2014) [BB]We discuss below how dietary phytochemicals such as genistein and omega-  
607 3s, may help restore neurochemical homeostasis including dopamine and glutamate .

608

609

610 **Norepinephrine**, also known as noradrenaline, plays a significant role in attention, arousal, and the  
611 modulation of executive functions. Alterations in norepinephrine signaling have been associated with  
612 ADHD (O'Donnell et al. 2012), affecting the regulation of attention and response inhibition. The  
613 physiological changes induced by the binding of norepinephrine to its receptors involve the  
614 modulation of several cognitive and executive processes usually impaired in ADHD, supporting the  
615 monoaminergic hypothesis for ADHD pathophysiology.

616

617 **Serotonin** is involved in mood regulation, emotional processing, and impulse control. Reduced  
618 levels of serotonin may contribute to the development of ADHD, influencing hyperactive and  
619 impulsive components of ADHD but perhaps not inattention (Banerjee and Nandagopal 2015). The  
620 involvement of serotonin in ADHD is supported by findings that reduced levels of the  
621 neurotransmitter may contribute to the disorder along with several genetic markers(Oades 2010).  
622 Identifying neurotransmitter interplay with ADHD is confounded by the many comorbidities of  
623 ADHD where more than 80 percent may exhibit co-morbid psychiatric problems and over half  
624 express symptoms satisfying two or more co-morbid disorders (Cumyn, French, and Hechtman  
625 2009).

626

## 627 *Emotional Dysregulation and ADHD*

628

629 Emotional dysregulation is also a major factor of ADHD with a growing body of research  
630 recognizing **emotional dysregulation** as a **core but underacknowledged component** of the  
631 condition, estimates suggest that **25–45% of children** and **30–70% of adults have this**  
632 **commodity** (Shaw et al. 2014) .

633

634

635

Oxytocin levels have also been implicated in ADHD study subjects correlating to clinically  
significant emotional dysregulation, including, aggression, and impaired empathy(Hwang et  
al. 2024).

636

637

638 Below we summarise the key neurotransmitters implicated in cognition, mood and ADHD  
639 symptoms and their key precursors and cofactors.

Neurotransmitter	Primary Role(s)	Key Precursors / Cofactors	Best BRAIN Diet Food Sources	Timing / Synergy Notes
<b>Glutamate</b>	Principal excitatory neurotransmitter; learning, memory, cognition and mood deficits	Glutamine (from protein), B6, magnesium, zinc	Lentils, poultry, fish, spinach, pumpkin seeds	Maintain magnesium & antioxidant intake to prevent excitotoxicity; balance with GABA-supporting foods in evening
<b>Dopamine</b>	Attention, motivation, executive function; DMN-to-task switching	Tyrosine, phenylalanine; iron, B6, folate, omega-3s	Lean poultry, beef, fish, dairy, soy, pumpkin seeds; omega-3 rich fish	Protein-rich breakfasts; pair with anti-inflammatory nutrients to protect DMN switching; avoid chronic over-reward from ultra-processed foods
<b>Norepinephrine</b>	Attention, arousal, executive modulation	Tyrosine, phenylalanine; vitamin C, copper	Same as dopamine sources + citrus, bell peppers (vitamin C)	Morning/midday higher-protein meals to support focus; avoid excessive stimulants late day
<b>Serotonin</b>	Mood regulation, emotional control, impulse moderation	Tryptophan; B6, magnesium; carb co-ingestion to aid LAT1 transport	Turkey, eggs, dairy, soy, seeds, oats, bananas	Pair tryptophan-rich proteins with moderate carbs to increase Trp:LNAAs ratio; timing midday or evening for calming effect
<b>GABA</b>	Main inhibitory neurotransmitter; calms neural activity, supports sleep	Glutamate (from protein), B6, magnesium, theanine	Green tea, fermented foods, spinach, almonds, pumpkin seeds	Increase intake later in day; combine with relaxation rituals for circadian alignment
<b>Acetylcholine and choline</b>	Memory, learning, neuroplasticity	Choline, acetyl-CoA	Egg yolks, fish roe, soy, wheat germ, liver	Regular choline intake supports ongoing synthesis; important for structural membrane health
<b>BDNF(modulator)</b>	Neurogenesis, synaptic plasticity, mood resilience	Omega-3s, polyphenols, exercise	Fatty fish, blueberries, turmeric, green tea, walnuts	Exercise + omega-3 + polyphenol synergy boosts expression; anti-inflammatory diet helps sustain levels

Neurotransmitter	Primary Role(s)	Key Precursors / Cofactors	Best BRAIN Diet Food Sources	Timing / Synergy Notes
Oxytocin(modulator)	Social bonding, trust, emotional buffering	Indirect (via gut–vagus axis, social cues)	Fermented foods, magnesium-rich foods, foods supporting dopamine & serotonin	Mindful shared meals, probiotic-rich foods, stress reduction; benefits from healthy dopamine tone

643  
644

Table X – Summary of ADHD implicated Neurochemicals

645  
646

#### 647 ***Key Neurotransmitter Strategies***

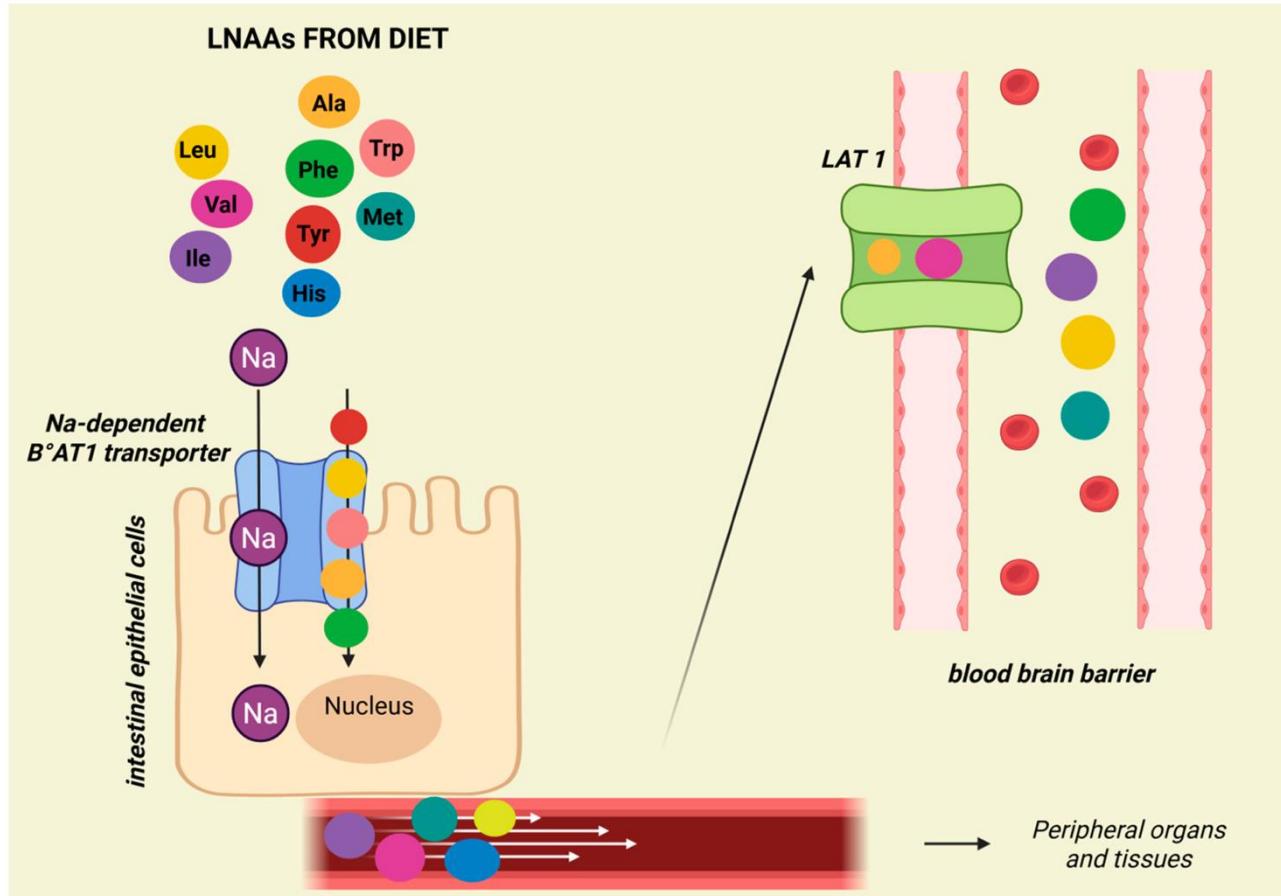
648  
649 Tryptophan, a serotonin precursor, has been linked to reduced anxiety, improved mood, and lower  
650 depressive symptoms (Aquili, 2020a), but shows very limited benefit for ADHD symptoms (Dinu et  
651 al., 2023). Its entry into the brain occurs via the LAT1 transporter and competes with other large  
652 neutral amino acids (LNAs) (tyrosine, phenylalanine, leucine, isoleucine, valine).  
653 Carbohydrate-rich, low-protein meals raise the plasma tryptophan:LNA ratio, because insulin  
654 pushes the competing LNAs out to muscles, lowering competing LNAs in plasma, thereby  
655 reducing competition at the BBB In a crossover breakfast study (Wurtman et al. 2003) (Wurtman et  
656 al. 2003):

- 657  Compared to the high protein breakfast, the high carbohydrate low protein breakfast raised the  
658 tryptophan:LNA ratio by a median ~54% (range ~36–88%).
- 659  Compared to the high carbohydrate breakfast, the high protein breakfast raised the tyrosine:LNA ratio  
660 by a median ~28% (range ~10–64%).

661 (

662 Carbohydrate type also matters: sucrose produced a larger rise in tryptophan:LNA (+34%)  
663 than starch (+20%), consistent with higher-GI carbohydrates more strongly enhancing brain  
664 tryptophan bioavailability (Lyons and Truswell 1988)(Lyons and Truswell 1988)).

666



667

668

Figure 3 – Increasing Tyr + Trp over LAT1 with Carb loading

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674

Tyrosine may enhance working memory performance in healthy older adults, potentially through modulating functional connectivity in brain regions associated with cognitive control (Hensel et al. 2019). Meta analysis of L-tyrosine have shown efficacy in some studies; other small studies suggested a quick tolerance after limited efficacy of only 2 weeks (F W Reimherr and M Ward 1987) suggesting that extra tyrosine will not fix a dopamine dysregulation problem and moreover that dopamine dysregulation is not the only ADHD problem.

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680

**BDNF** - Low levels of BDNF have been associated with various neurodevelopmental disorders, including the polymorphism Val66me which has been linked with lower dopamine and lower BDNF and correlated to anxiety and depression (Hünnerkopf et al. 2007). Knowing one's Val66Met status, via genetic testing, can inform personalized plans for exercise, dietary factors i.e. omega-3s which also can increase BDNF (Ziae et al. 2024).

681

## Cholinergic systems

682

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686

Choline, while not an amino-acid, is commonly found in protein-rich foods and plays a crucial role in acetylcholine synthesis and membrane integrity in neurons. Choline has had a positive effect on ADHD in studies (Derbyshire and Maes 2023). There are recent studies now targeting imbalances in the cholinergic systems representing a new focus in ADHD etiology (Johansson et al. 2013).

687  
688  
689

## GABAergic ( $\gamma$ -aminobutyric acid)- system

690 (GABA), the most abundant inhibitory neurotransmitter in the central nervous system (CNS). While  
691 the GABAergic system has not traditionally been implicated as a main cause of ADHD, many studies  
692 have proven ADHD subjects have reduced GABA concentration compared with control subjects  
693 (Edden et al. 2012) suggest impaired inhibitory tone and potential sleep disruption, contributing  
694 towards hyperactivity (Puts et al. 2020).

695 Circuit-level dysregulation of GABA, particularly involving excitation–inhibition (E/I) imbalance,  
696 has been linked to neurotransmitter crosstalk, showing the pleiotropic nature of  
697 neurotransmitters. For example how the excitatory glutamate transmitter binds to the inhibitory  
698 GABAA receptor, thereby allosterically potentiating its inhibitory function. (A. Chai 2025).  
699 (Mamiya et al. 2021) propose E/I balance as a candidate biomarker for ADHD, stating the  
700 development of GABA modulating interventions as high potential candidates.

701 Supporting GABA synthesis, signaling, and receptor modulation through dietary inputs may provide  
702 a novel, underexplored avenue for intervention. Key contributors include:

- Vitamin B6 – cofactor for glutamate decarboxylase, essential for converting glutamate to GABA.
- Magnesium – functions as an NMDA receptor antagonist and GABA receptor modulator ((Clerc et al. 2013)).
- Zinc – acts as an allosteric modulator of the GABA receptor ((Peralta and Huidobro-Toro 2016));).
- Functional amino acids – taurine, glycine, and theanine enhance inhibitory signaling.
- Fermented foods – provide exogenous GABA and microbiota-mediated GABA precursors.
- Polyphenols – compounds such as genistein have been directly linked to GABA modulation.

712

### ***Implications for Dietary Strategy***

713 GABA is one example how the broad food matrix support for neurotransmitters is key in creating  
714 overall neurotransmitter production balance and potentially bringing better E/I balance to improve  
715 ADHD symptoms. Targeting regular dietary neurotransmitter precursors and cofactors should have a  
716 positive effect on cognition and ADHD symptoms such as attention and hyperactivity.

718

### ***Looking beyond dietary strategies for neurochemical support***

719 Although not traditionally considered a target in ADHD treatment, oxytocin has been linked also to  
720 reducing impulsivity in ADHD while studies have also found dopamine levels involved in ADHD  
721 etiology impair oxytocin levels in children with ADHD(Esra DEMİRCİ 1 2016). The modulation of  
722 oxytocin through diet, lifestyle, and social connection represents a promising avenue for holistic  
723 lifestyle and dietary support. The BRAIN Diet promotes endogenous oxytocin production through  
724 lifestyle strategies like mindful meals and shared eating, fermented foods that support the gut and  
725

726 vagus signaling, and by reinforcing a neurobiological foundation of stress reduction and emotional  
727 buffering thus preventing relapse into dysregulation.

728  
729

## 730 **5. Fats: Omega-3 & Brain-Healthy Fats**

731

### 732 ***The Role of Fats in Brain Function***

733 Fats, or dietary lipids, are a fundamental pillar of brain health, influencing everything from  
734 membrane composition to inflammatory tone and neurotransmitter regulation. This section looks at  
735 omega-3 specifically but below we also cover fats which help minimise oxidation in cooking or fats  
736 that introduce antioxidants and other nutrient rich substances like CoQ10 in extra virgin olive oil.  
737 Many other fats offer great nutritional value are commonly overlooked such as duck fat, MCT oil,  
738 and certain nuts, and avocado (see table 4 below).

### 739 ***Cardiovascular Guidelines and Relevance to Brain Health***

740 Dietary guidelines from the World Health Organization and the Dietary Reference Intakes  
741 recommend a total fat intake between 20 and 35% of total calories(A. G. Liu et al. 2017) , with the  
742 NHS stating 30g limit of saturated fats per day for males and 20g for women and not more than 5g of  
743 transfats per day. (NHS.gov 2023). A 30 year longitudinal study (Yanping Li et al. 2015) found that  
744 replacing 5% of energy intake from saturated fats with equivalent calories from PUFAs,  
745 monounsaturated fats, or whole grain carbohydrates was associated with a 25%, 15%, and 9% lower  
746 risk of coronary heart disease (CHD), respectively.

747 Further guidance and clinical guideline averages of daily values:

- 748 • **Monounsaturated fats (MUFA) — ~10–15%**  
749 Sources: extra-virgin olive oil, avocado, olives, nuts.
- 750 • **Omega-3 (PUFA) — ~1–2% and 250–500 mg EPA+DHA/day (RCT variations: 500–2000**
- 751 **mg/day)**
- 752 • **Saturated fat (SFA) — <10% (ideally <7%)**  
753 Note: some short-/medium-chain SFAs may have niche metabolic roles. Sources: dairy fat,  
754 meat, coconut.
- 755 • **Trans fats — 0%**  
756 Eliminate industrial trans fats; avoid “partially hydrogenated oils” on labels.

757

758 The bidirectional link between heart health and brain health is well documented. Poor cardiovascular  
759 function is associated with impaired stress responses, reduced cognitive performance, and increased  
760 risk of Alzheimer's disease. ADHD itself has been correlated with higher CHD risk (L. Li et al.  
761 2022), though meta-analyses highlight the need for better-controlled studies due to key confounding  
762 factors not being controlled such as exercise and diet . However, when designing a diet targeting  
763 brain health, cardiovascular protection remains a critical co-priority.

764 ***Reframing Saturated Fat: miconutrient specifics***

765 The BRAIN Diet prioritizes fats that reduce inflammation, support membrane integrity, and optimize  
 766 cognitive performance, rather than enforcing blanket restrictions on all sources of saturated fat or  
 767 cholesterol. While excessive intake is linked to cardiovascular risk, both nutrients serve critical  
 768 physiological roles, with cholesterol being essential for synapse formation, myelin integrity, and the  
 769 production of steroid-based neurohormones (Pfrieger 2003).<sup>1</sup>

770 Instead of excluding them, dietary strategies should focus on unprocessed, nutrient-dense sources  
 771 such as Parmesan cheese, grass-fed butter, and pasture-raised egg yolks. When consumed in  
 772 moderation within an anti-inflammatory, micronutrient-rich diet, these foods can provide essential  
 773 brain nutrients including choline, vitamin K2, butyrate, and fat-soluble vitamins A, D, and E. Beyond  
 774 just the wide array and vitamins and minerals there are a wide array of powerful and proven nutrients  
 775 which are still underresearched but have great potential (Table 4.) i.e. C15:0 (Parmesan and  
 776 grassfed Butter), astaxanthin (Fish roes), moreover as we consider the wider implications of the  
 777 food matrix, studies have shown that hard cheeses with high calcium do not raise serum LDL  
 778 levels (Soerensen et al. 2014).

779

Fat Source	Key Nutrients & Benefits *Note all nutrients will vary by producer, by batch and season	Best Uses
1. Salmon Roe	DHA, EPA, phospholipids, choline, astaxanthin; highly bioavailable; zero oxidation risk	Cold dishes, sushi, spoonful daily
2. Grass-Fed Butter	Butyrate, Conjugated linoleic acid (CLA; such as rumenic acid), vitamins A/D/K2, selenium, C15:0 pentadecanoic acid	Finishing veg, grains, or cooking (with higher smoke point oil to avoid burning)
3. Duck Fat	Oleic acid, selenium, palmitoleic acid (anti-inflammatory MUFA)	Roasting vegetables, pan cooking
4. Extra Virgin Olive Oil	Oleic acid, coQ10, hydroxytyrosol, squalene; strong antioxidant & anti-inflammatory profile	Salad dressings, drizzling, low-heat
5. Avocado / Avocado Oil	MUFA (oleic), vitamin E, lutein, fiber, glutathione	Spread, salads, oil for dressing
6. Coconut Oil / MCT Oil	MCTs (C8, C10), rapid energy for brain, supports ketone production	Smoothies, baking, small-portion use
7. Parmesan Cheese	CLA, vitamin K2, glutamate, high protein, calcium; fermented, C15,	Grated topping, snacks
8. Seaweed (Whole)	Glycolipids, EPA (in red algae), iodine, magnesium, fiber	Added to soups, stews, or salads
9. Algal Oil (Supplement)	Vegan DHA (from microalgae), used in infant formulas, neuroprotective	Liquid or capsule (not culinary)
10. Ghee	Butyrate, vitamins A/D/E/K2, heat-stable, low in lactose/casein	High-heat cooking, Ayurvedic dishes

780 **Table 4 - high nutritional value fats**

781 Fats to avoid

Fat Type	Concern	Where Found
Refined Seed Oils	High omega-6, low oxidative stability, disrupt omega-3 balance	Soy, corn, sunflower, canola (refined)
Artificial Trans Fats	Linked to cognitive decline, neuroinflammation, and metabolic disorders	Ultra-processed foods, cheap margarines

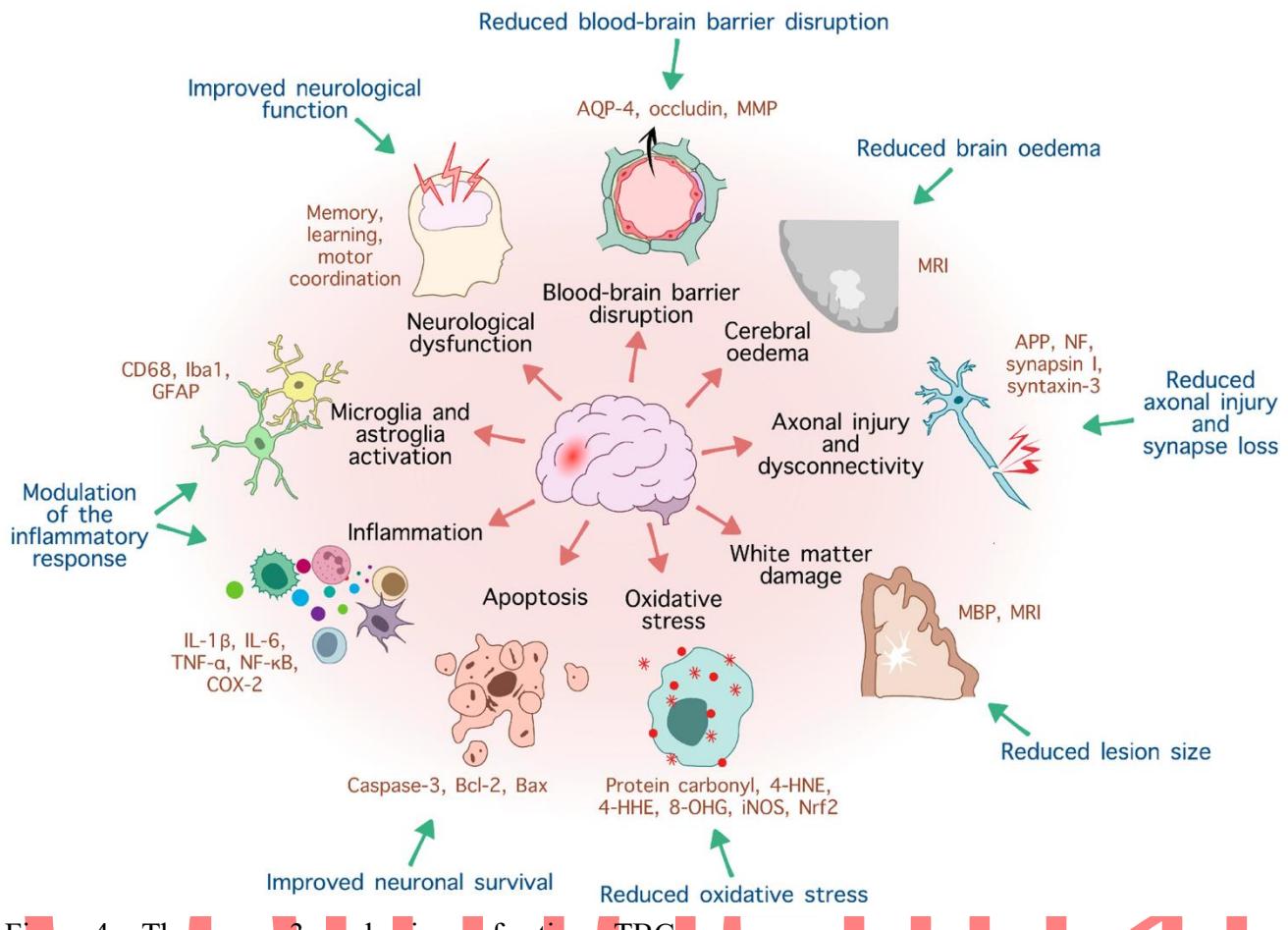
782 **Table 5 – Fats to be avoided or limited**

783 **3.1 Omega 3 Mechanisms of Action and success factors**

784 LClick or tap here to enter text.ipids constitute 50–60% of dry weight of mature human brain with  
785 35% of these comprising of PUFA with long chain (LC-PUFA) PUFA n-6 content reaching 17%  
786 (mainly Arachidonic Acid) and the content of PUFA n-3 DHA was as much as 14%, depending upon  
787 the brain region (McNamara and Carlson 2006).

788 Omega-3 fatty acids, particularly EPA and DHA, exert multifaceted effects on brain function that  
789 extend beyond their structural roles in neuronal membranes. Their actions influence gene expression,  
790 neurotransmission, inflammation resolution, and synaptic plasticity through a network of interrelated  
791 pathways. . These include modulation of nuclear receptor signaling through PPAR proteins, support  
792 for phospholipid membrane dynamics, and the generation of specialized proresolving mediators  
793 (SPMs) that downregulate inflammatory responses.

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795  
796  
797  
798  
799 Figure 4 – The omega 3 mechanisms of action - TBC  
*Success Factors*

### **Balance DHA/EPA and Omega-3/Omega-6 Balance**

800 The balance between omega-3 and omega-6 fatty acids plays a key role in regulating inflammation..  
 801 While arachidonic acid (AA), an omega-6 PUFA, gives rise to mostly pro-inflammatory eicosanoids,  
 802 omega-3s like eicosapentaenoic acid (EPA) and DHA are precursors to anti-inflammatory SPMs such  
 803 as resolvins, maresins and protectins. Western diets can skew this ratio as high as 20:1 in favor of  
 804 omega-6s, contributing to chronic inflammation and neurotransmitter dysregulation (Simopoulos  
 805 2011) while also increasing blood viscosity, vasospasm, and vasoconstriction which may play a  
 806 major role in inducing autoimmune, cardiovascular and neurological diseases. (Simopoulos 2009).  
 807

808 Most research showing brain function improvements lean towards higher ratio of EPA to DHA (e.g.,  
 809 2:1 ratio or higher though Stonehouse et al used a DHA dominant dose) with DHA having a more  
 810 structural role in the brain and EPA with a more functional role. (McNamara and Carlson 2006) One  
 811 meta study (Pei-Chen Chang 2021) (Stonehouse et al. 2013). Phospholipid Transport and DHA/EPA  
 812 Delivery across the Blood Brain Barrier.

813  
 814 Phosphatidylcholine (PC) is a key carrier of DHA and EPA to the brain. DHA or EPA incorporated  
 815 into PC and converted into lysophosphatidylcholine (LPC) which crosses the blood-brain barrier  
 816 (BBB) far more efficiently than its free fatty acid or triglyceride-bound forms (Patrick 2019).

Studies show phospholipid-bound omega-3s such as krill oil and fish roe, provide EPA/DHA in a phospholipid form that gets converted to LPC.s, (L. Liu et al. 2014) . Krill oil is also a favored food source of DHA and EPA since it is low in the food chain, does not concentrate environmental toxins or heavy metals (Colletti et al. 2021)(Patted et al. 2024)

## ***Mechanisms of Action of omega-3***

822

## ***Specialized Pro-Resolving Mediators and Inflammation Resolution***

Specialized pro-resolving mediators (SPMs), derived from omega-3s, play an active role in terminating inflammation without suppressing immune surveillance. These include resolvins, protectins, and maresins, which exert effects such as inhibition of neutrophil infiltration, downregulation of COX-2, and enhancement of macrophage-mediated clearance of cellular debris (Serhan and Petasis 2011). Moreover, SPMs modulate endothelial function through nitric oxide release and support neuroprotection by limiting glutamate-induced excitotoxicity and promoting regulatory T-cell differentiation (Briones et al. 2025). Although inflammation typically isolates tissues that have been injured or infected and begins the repair of an injury it is important to resolve and end the inflammatory response. SPMs are lipids that accomplish this without generalized immunosuppression.

835

## ***Membrane Phospholipids, Ion Channels, and Gamma Activity***

Omega-3s such as docosahexaenoic acid (DHA) and structural fats like linoleic acid contribute to neuronal membrane fluidity, neurogenesis and neuroplasticity (Crupi, Marino, and Cuzzocrea 2013). Phospholipid methylation (PLM), a process enhanced by dopamine D4 receptor activity, a key gene implicated in ADHD (Martel et al. 2011), alters the structure of membranes, facilitating faster neuronal recovery while influencing ion channel behavior in the generation of gamma oscillations, brainwaves linked to attention and cognition. Abnormalities in membrane composition and PLM have been linked to impaired ion channel regulation and reduced gamma-band activity in ADHD ((Cocchi et al. 2017) (Wilson et al. 2012)). Phospholipid methylation, dependent on SAMe, directly affects membrane fluidity and neurotransmitter receptor function. Maintaining optimal intake of phospholipid precursors, choline, methionine, and serine, may support PLM and cognitive performance.

## ***Endocannabinoid System Dysregulation & N-Acyl Lipid Signaling***

The endocannabinoid system (ECS) is a key neuromodulatory system that helps regulate dopamine signaling(Covey et al. 2017) and motivation(Laksmidewi and Soejitno 2021), stress response, and inflammation, processes that are often disrupted in ADHD and other neurodevelopmental conditions. A major pathway supporting this system is the CDP-ethanolamine pathway, which produces phosphatidylethanolamine (PE)—a key brain phospholipid and potential ADHD biomarker. PE can be converted into phosphatidylcholine (PC) or N-acyl phosphatidylethanolamines (NAPEs)(Garani, Watts, and Mizrahi 2021). These NAPEs are precursors to N-acyl ethanolamines (NAEs) like palmitoylethanolamide (PEA), oleoylethanolamide (OEA), and anandamide (AEA), bioactive lipids which act as neuromodulators with anti-inflammatory, neuroprotective, and mood-regulating effects.

858 High plasma levels of AEA have been correlated to psychotic disorders and lower levels to Major  
859 Depressive Disorder(Garani, Watts, and Mizrahi 2021) while higher levels have also been associated  
860 with ADHD (Brunkhorst-Kanaan et al. 2021).

861 Supporting NAPEs production through diet via PE-rich foods like eggs, fish roe, and liver may  
862 enhance ECS tone. Clinical trials have shown a doubling of plasma levels after dietary increases in  
863 oat bran due to it's rich PE content (Sean Davies 2018). Polyphenols such as genistein may further  
864 enhance ECS tone by inhibiting fatty acid amide hydrolase (FAAH), the enzyme responsible for  
865 AEA degradation (Gibellini and Smith 2010).

866 Additionally, polyphenols such as genistein may help preserve AEA levels by inhibiting fatty acid  
867 amide hydrolase FAAH, the enzyme that breaks down AEA (Gibellini and Smith 2010). So by  
868 preserving anandamide, Genistein may amplify the ECS's ability to regulate dopamine(Bare, Ghetti,  
869 and Richter 1995), glutamate, and GABA signaling (Huang, Fang, and Dillon 1999) all key pathways  
870 to regulate in ADHD.

871 Although omega-3s are not direct endocannabinoids, they contribute to endocannabinoid-like  
872 signaling through the production of docosahexaenoyl ethanolamide (**DHEA**) , EPEA(Watson, Kim, and  
873 Das 2019), and other N-acyl ethanolamines, and can indirectly affect ECS system. While more  
874 research on the endocannabinoid pathways and ADHD is needed, its interactions with dopamine,  
875 mood regulation, and inflammation make it a relevant secondary target, particularly in cases of  
876 emotional dysregulation or stress sensitivity.

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## *Considerations and Safety of Omega-3 Supplementation*

880  
881 Finally, although omega-3 supplementation is generally safe, a meta-analysis has reported a modestly  
882 increased risk of atrial fibrillation in individuals with predisposing cardiovascular conditions  
883 receiving high-dose omega-3 supplements, indicating the need for individual risk stratification ( f et  
884 al. 2021).  
885

### **3.2 Homocysteine, Methylation, and Cognitive Function**

886  
887  
888 Methylation processes are central to neurotransmitter synthesis, membrane remodeling,  
889 detoxification, and epigenetic regulation, all of which are relevant in the context of ADHD and  
890 cognition. B vitamins, particularly B6, folate (5-MTHF), and B12, are essential cofactors in the  
891 remethylation of homocysteine (Hcy) to methionine, which is subsequently converted to S-  
892 adenosylmethionine (SAMe), the universal methyl donor. One study with 3 groups taking  
893 supplementations of 1: vitamin B-12, 2: fish oil, and 3:vitamin B-12+fish oil, lowered plasma Hcy  
894 concentrations by 22%, 19%, and 39%, respectively (Tao Huang, n.d.). The VITACOG trial further  
895 demonstrated that B vitamin supplementation slowed cognitive decline only in participants with  
896 adequate omega-3 status (Oulhaj et al. 2016)

897  
898 Elevated plasma homocysteine a byproduct of methylation, is elevated in ADHD and other  
899 neurodegenerative diseases (Yu et al. 2020), (Luzzi et al. 2022), cognitive impairment, and  
900 psychiatric conditions (Lukovac et al. 2024a). Hcy is implicated in the induction of oxidative stress,  
901 the modulation of oxygen levels, and the initiation of lipid peroxidation pathway(Lukovac et al.  
902 2024b).

903 Trimethylglycine (TMG), also known as betaine, is a dietary methyl donor that helps recycle Hcy to  
904 methionine via an alternative pathway. Choline, a precursor to both TMG and phosphatidylcholine  
905 (PC), is similarly involved in homocysteine clearance and, as discussed above, membrane  
906 phospholipid biosynthesis. These pathways are vulnerable to genetic variants such as MTHFR  
907 polymorphisms, which reduce the efficiency of folate cycling and methylation, thereby increasing  
908 susceptibility to cognitive dysfunction and ADHD-related symptoms.

909

## 910 **6. Carbohydrates , Fibre-Rich Foods for Gut Health**

### 911 ***Brain Fuel and Complex Carbs for a Healthy Gut Biome***

912 Carbohydrate selection is critical to regulating core biological processes relevant to brain function.  
913 Poor carbohydrate choices may contribute to insulin dysregulation, inflammation, obesity, and other  
914 metabolic disorders (Cho and Choi 2021) Because the brain has limited capacity to store energy,  
915 maintaining a steady supply of glucose is essential for optimal cognitive function, unless a ketogenic  
916 dietary pattern is being followed , and risks have to be carefully assessed.(Crosby et al. 2021)

### 917 ***Resistant Starches***

918 The inclusion of complex carbohydrates and fermentable fibers plays a central role in supporting  
919 metabolic health and brain function. Complex carbohydrates consist of long chains of sugar  
920 molecules—such as starch and fiber, that digest more slowly, providing a steady release of glucose.  
921 Key sources include whole grains (like pseudo grains like quinoa and buckwheat, grains like barley  
922 and oats), fibrous vegetables, and legumes such as lentils and chickpeas. In parallel, both **soluble**  
923 **fiber** (from apples, oats, flaxseeds) and **insoluble fiber** (from vegetables, nuts, and whole grains)  
924 support digestive health, glycemic control, and microbial diversity, factors increasingly linked to  
925 improved cognition, emotional regulation, and long-term neuroprotection (Massimino et al. 1998).

926 The complex carbohydrate, Resistant Starch, forms when certain starchy foods are cooked and then  
927 cooled, a process called retrogradation. Foods like rice and potatoes develop higher resistant starch  
928 content when chilled, and reheating does not reverse this effect one example i.e. white rice was  
929 cooled and reheated showing a rise in RS content from 0.64 to 1.65 g/100 g and elicited a lower  
930 glycemic response(Yunting Li et al. 2024).

931 These indigestible starches are fermented by gut bacteria in the colon, producing short-chain fatty  
932 acids (SCFAs) such as butyrate, which help maintain gut barrier integrity, reduce systemic  
933 inflammation, and influence brain function through immune, endocrine, and vagal pathways(Zhou et  
934 al. 2015).

935

936 **5.1 Possibilities and Challenges with Gut microbiome science**

937 A growing body of evidence suggests that modulating the gut microbiome can positively influence  
938 brain health and overall health. The gut is central in producing neurotransmitters, reducing systemic  
939 inflammation, and enhancing gut-brain axis communication.

940 The gut microbiome's two dominant bacterial phyla are Firmicutes and Bacteroidetes, and their  
941 relative abundance (the Firmicutes:Bacteroidetes (F/B) ratio) is often considered a broad indicator of  
942 gut "balance" or dysbiosis. (Schleupner and Carmichael 2022). Studies have shown how by  
943 increasing the diversity of taxa can increase the possibilities for individuals to produce certain health  
944 beneficial metabolites such as Urolithin A (Schleupner and Carmichael 2022), or increase omega 3  
945 metabolism (Zinkow et al. 2024) and reduce down stream harmful gut metabolites (Brown, Clardy,  
946 and Xavier 2023).

947

948 Studies have shown conflicting results in categorising micro biata of ADHD subjects and in general  
949 the taxonomy is still evolving. (Wang et al. 2024) noted reduced levels of beneficial bacteria such as  
950 Faecalibacterium prausnitzii and Bifidobacterium, but conversely (Aarts et al. 2017) found that  
951 individuals with ADHD had slightly increased Bifidobacterium. Aarts highlighted that just naming a  
952 genus like Bifidobacterium doesn't reveal its functional impact i.e while one species produce anti-  
953 inflammatory SCFAs; another they found spiked phenylalanine levels; the key is really dealing with  
954 gut bacteria at the strain level.

955

956 ***The gut brain axis***

957 The gut-brain connection may also play a significant role in the etiology of ADHD. Gut health  
958 influences neurotransmitter production (e.g. serotonin, gamma-aminobutyric acid (GABA) and  
959 dopamine). Even though gut produced neurotransmitters passing the Blood Brain Barrier (BBB) is  
960 not confirmed in human studies, the precursors for neurotransmitters do cross the blood brain barrier  
961 so that neurotransmitters can be produced in the brain directly. It is also understood that the Vagus  
962 Nerve sends signals to the brain so gut based neurotransmitters can affect mood and motivation; with  
963 vagal nerve stimulation having been proven in many therapeutic areas already(Austelle et al. 2022),  
964 though many studies which illucidate clinical revlevance remain in preclinical models(Bravo et al.  
965 2011).

966

967 ***Prebioics and probiotics***

968 Interventions such as prebiotics, probiotics, high-fiber diets, and fermented foods, collectively  
969 referred to in emerging research as *psychobiotics*, have been associated with changes in attentional  
970 vigilance(Schmidt et al. 2015) and mood regulation and reduced anxiety and cortisol (Johnstone et al.  
971 2021). These effects are thought to be mediated through increased production of short-chain fatty  
972 acids (SCFAs) like butyrate, which support intestinal barrier integrity, regulate immune responses,  
973 and promote the synthesis of key neurotransmitters such as dopamine and serotonin(Silva et al.  
974 2020). While more large-scale clinical trials are needed, current research supports the gut  
975 microbiome as a promising, non-invasive target for adjunctive ADHD treatment.

976

977

978 **Short-Chain Fatty Acids (SCFAs)**

979

980 Diets rich in **probiotics, prebiotics, and fiber** (which help produce short-chain fatty acids like  
981 butyrate, **Propionate and lactate**) can enhance gut health. Furthermore, a decreased microbial  
982 diversity (alpha diversity) has also been reported in ADHD (Prehn-Kristensen et al. 2018) and may  
983 contribute to ‘leaky gut’ syndrome and contribute to the low-grade systemic inflammation reported  
984 in ADHD.

985 These are byproducts of fiber fermentation in the gut and have been linked to improving brain  
986 function via either the gut-brain axis or in some cases such as Butyrate by crossing the blood brain  
987 barrier. SCFAs play a crucial role in various physiological processes, including maintaining gut  
988 health, modulating the immune system, and influencing brain function. A recent study (Steckler et al.  
989 2024) showed the ADHD group exhibiting significantly lower levels of key SCFAs, including acetic,  
990 propionic, isobutyric, isovaleric, and valeric acids, highlighting a distinct microbial and metabolic  
991 profile.

992 **Butyrate:** Butyrate and other SCFA deficiencies have been linked to many neurological  
993 disorders(Deng et al. 2019) including ADHD (Fan et al. 2019)but many of the studies are not in-  
994 human studies or have been noted for other confounding factors in study design despite some  
995 sensible stratification of study subjects (Checa-Ros et al. 2021; Kurokawa et al. 2024). Butyrate  
996 deficiencies where also linked to ASD and melatonin production and loosely inferred to have  
997 relevance in ADHD populations due to symptom cross over and disorder pathways.

- 998 • **Sleep Disorders:** (Checa-Ros et al. 2021b) Also linked butyrate deficiencies to also  
999 melatonin production and ASD, while loosely inferring relevance to ADHD  
1000 populations due to symptom cross over and disorder pathways. Sleep deprivation and  
1001 low melatonin were also associated with a significant decrease in microbial diversity  
1002 and richness. Sleep disorders can be present in up to 70% of ADHD patients so they  
1003 represent one of the most frequent comorbidities in children with ADHD(Cortese et  
1004 al. 2009) underscoring the potential of gut biome diversity and butyrate levels.
- 1005 • **Neuroinflammation Reduction:** Butyrate has anti-inflammatory effects, potentially  
1006 reducing neuroinflammation associated with ADHD (Yunting Li et al. 2024)
- 1007 • **Energy Metabolism:** Butyrate supports mitochondrial function, enhancing brain  
1008 energy metabolism, which may help with cognitive impairments seen in ADHD (Rose  
1009 et al. 2018) while also aiding in reducing cholesterol and neuroinflammation  
1010 (Cavaliere et al. 2022).

1011 **Propionate** research suggests that increased propionate levels could help reduce  
1012 neuroinflammation(Grüter et al. 2023) and enhance cognitive function while protecting the blood-  
1013 brain barrier (Hoyles et al. 2018) and stimulate the secretion of norepinephrine, possibly benefiting  
1014 ADHD symptoms like attention and focus.

- 1015 • Additionally, propionate might influence dopamine regulation (Mirzaei et al. 2021),  
1016 which plays a role in reward processing and impulsivity, key areas affected in ADHD.

1017 **Bifidobacterium.** A lowered abundance of *Bifidobacterium longum* in infancy has been associated with  
1018 increased risk of developing ADHD and Asperger syndrome in childhood.(Pärty et al. 2015). The same  
1019 study also showed early administration of *Lactobacillus rhamnosus GG* may reduce the risk of  
1020 ADHD and AS. A small study showed significant improvements in children's inattention and  
1021 hyperactivity with supplements of (Pivac et al. 2011) while the study also noted significant negative  
1022 correlations between N-Glycan biosynthesis; which is consistent with an indepth study of  
1023 glycosylation abnormalities in ADHD. (Pivac et al., 2011).

1024

1025  
1026 **Lactobacillus** was shown to produce acetylcholine in a study dating back to 1947(Stephenson,  
1027 Rowatt, and Harrison 1947) and such strains have also been shown to be effective against Alzheimer's  
1028 disease induced rat models(Nimgampalle 2017).

1029

1030 Several species in the *Lactobacillus* genus (recently reclassified into multiple genera) other popular  
1031 strains used in medical research include: **Rhamnosus GG** (L GG) which has been shown to stabilize  
1032 the gut permeability barrier by mucin production and antigen-specific immunoglobulin A production.  
1033 (Khailova et al. 2017) In addition, a recent experimental study has demonstrated that *Lactobacillus*  
1034 *rhamnosus* regulates, again via the vagus nerve, emotional behavior and the influences the central  
1035 GABAergic system and serotonin (Bravo et al. 2011):

1036

1037

1038 **Levilactobacillus brevis** is one of the key bacteria known to produce GABA. It produces GABA through  
1039 the glutamate decarboxylase (GAD) pathway , where it converts glutamate into GABA (Cataldo et al. 2024).  
1040 This bacteria is active in *L. brevis* strains isolated from fermented foods, such as kimchi, yogurt, and  
1041 pickles. One isolated strain, CRL 2013 (Kim et al. 2009), found in quinoa sourdough(Chiş et al. 2020),  
1042 had very high nutrient and GABA profile.

1043

1044

Mineral	Content in Sourdough (mg/100 g)	RDA/AI for Adults (mg/day)	% of RDA per 100 g
GABA	~265 mM	No applicable  Ranges 50-3,000 milligrams, per day; Not to exceed 750 milligrams per single dose(Oketch-Rabah et al. 2021)	
Calcium (Ca)	18,09	1000	1.8%
Magnesium (Mg)	303,43	310	72-98%

Potassium (K)	813,92	2600	24-31%
Iron (Fe)	3,02	8	17-38%
Copper (Cu)	0,96	0,9	107%
Zinc (Zn)	1,82	11	17-23%
Manganese (Mn)	2,5	2,3	109-139%
Chromium (Cr)	n.d.	0,035	

1045

1046 Table 7 – High nutrient content of GABA rich Qinoa sourdough

1047

1048 Faecalibacterium is known for its anti-inflammatory properties. The scarcity of this genus could  
 1049 potentially lead to overproduction of pro-inflammatory cytokines, which aligns with the high levels  
 1050 of pro-inflammatory cytokines found in children with ADHD and it's low levels correlating to  
 1051 ADHD symptoms in children(Jiang et al. 2018) and allergies such as Th2-mediated atopic disorders  
 1052 like asthma and allergic rhinitis, which when present in children were associated with a 30–50%  
 1053 higher chance of developing ADHD (Bull-Larsen and Mohajeri 2019).

1054

1055

1056 

## 7. Antioxidants (Oxidative Stress, Mitochondrial Health, NRF2 Activation)

1057

### *Antioxidant networks for increased protection*

1058

1059 While the body has multiple endogenous antioxidant defenses, including enzymes like superoxide  
 1060 dismutase and glutathione peroxidase, these can become overwhelmed in states of chronic  
 1061 inflammation, nutrient deficiency, or high metabolic demand. Lester Packer introduced the concept  
 1062 of the "antioxidant network(Packer et al. 1997)," detailing how key compounds like vitamin E,  
 1063 vitamin C, lipoic acid, glutathione, and CoQ10 have been shown to work synergistically and  
 regenerate each other in vivo.

1064

1065 The BRAIN diet will prioritize reducing dietary pro-oxidants and inflammatory triggers while  
 1066 introducing a wide spectrum of antioxidant-rich foods. This approach is particularly important for the  
 1067 brain, which consumes a disproportionate share of the body's oxygen and contains lipid-rich  
 1068 neuronal membranes that are highly susceptible to peroxidation. In neurodevelopmental conditions  
 1069 such as ADHD, there is increasing recognition that oxidative stress, mitochondrial dysfunction, and  
 1070 neuroinflammation contribute to cognitive, emotional, and behavioral dysregulation(A. A. J. Verlaet  
 et al. 2019) (Ogutlu, Kasak, and Tabur 2023).

1071

1072 Although high-dose antioxidant supplements have shown inconsistent or even harmful effects in the  
 1073 rare case of the Vitamin E clinical trials and prostate cancer(Klein et al. 2011), diets rich in natural  
 1074 antioxidant compounds have demonstrated robust benefits. The Green Mediterranean Diet DIRECT-  
 PLUS studies, led to significantly greater reductions in visceral adipose(Zelicha et al. 2022) and

1075 neuroprotective effects(Pachter et al. 2024)(Pachter et al. 2024). This effect was accompanied by  
1076 increases in microbiome-derived metabolites like urolithin A, reinforcing the synergistic role of  
1077 polyphenols, fiber, and gut-derived antioxidants in improving metabolic and cognitive resilience.

1078 The framework of the **BRAIN Diet** embraces:

- 1079
- 1080 • **The acknowledge of the theoretical strength** of the antioxidant network i.e. working many  
1081 different antioxidants into the diet and precursors for endogenous antioxidants
  - 1082 • Emphasize **food-based sources** rich in polyphenols, flavonoids, and balanced antioxidants.
  - 1083 • Avoid **promoting high-dose single-nutrient supplementation** unless there's clinical  
1084 justification and consultation and agreement with healthcare professionals
  - 1084 • Highlight **synergy in whole-foods**, not megadoses of any one food source.

1085 Isothiocyanates (ITCs) like sulforaphane, found in broccoli, have also shown promising results in  
1086 reducing oxidative stress and offering protection against various chronic diseases, including cancer  
1087 and cardiovascular disorders while also showing higher bioavailability than other polyphenol-based  
1088 dietary supplements that also activate Nrf2.(Houghton, Fassett, and Coombes 2016)

1091 ***Complex Antioxidant Networks and Mineral Cofactors***

1092 The antioxidant family also includes essential minerals that serve as cofactors for antioxidant  
1093 enzymes. Selenium, zinc, and manganese, for instance, are crucial for the proper functioning of  
1094 various antioxidant systems within the body(Moccagiani and Malavolta 2019). This intricate  
1095 network of antioxidants works synergistically (Vertuani, Angusti, and Manfredini 2004), with each  
1096 component complementing the others to maintain cellular health and prevent oxidative damage.

1097 Sourced from a wide variety of ‘functional foods’(Pouille et al. 2022), particularly fruits, vegetables,  
1098 nuts, and whole grains, antioxidants extend their mechanisms of action beyond simple free radical  
1099 scavenging to include metal ion chelation. Heavy metals are detoxified in the body by  
1100 metallothionein (MT) metal carrier proteins that must bind with Zn and copper (Cu) (Zhai et al.  
1101 2015)(Zhai et al., 2015), ADHD has been linked with metals contamination and UPFs which contain  
1102 among other additives high amounts of metals, particularly in food colourings; ADHD and other  
1103 neuropsychiatric disorders have been also linked to maternal food habits such as high UPF  
1104 consumption.(Dufault et al. 2024) . Besides heavy metals micro/nanoplastics (MNPs) are being  
1105 linked to many diseases, reproductive health and ADHD; (J. Zhang et al. 2025). Anthocyanins,  
1106 especially C3G-rich sources like **berries, purple potatoes, and black goji**, serve as:

- 1107
- 1108 • **Natural chelation agents** for heavy metals and environmental contaminants
  - 1109 • **Neuroprotective molecules** that support synaptic resilience and detox pathways
  - **Detox allies** against microplastics and hormone-disrupting pollutants

1110 Phenolic acids represent some of the most abundant antioxidants in plant-based foods, with whole  
1111 grains and bran being especially rich sources. Among these, ferulic acid stands out as a key  
1112 compound illustrating how food matrix effects translate into brain resilience. Processing methods  
1113 such as sprouting and fermentation release bound ferulic acid, enhancing bioavailability. Once  
1114 absorbed, it crosses the blood–brain barrier, scavenges reactive oxygen species, and synergizes with  
1115 vitamins C and E to stabilize neuronal membranes and preserve DHA. Such mechanisms highlight

1116 why dietary patterns emphasizing whole, minimally processed grains may deliver neuroprotective  
1117 effects beyond their macronutrient profile.

1118 Carotenoids, particularly lutein, zeaxanthin, and β-carotene, play a neuroprotective role through their  
1119 antioxidant and anti-inflammatory properties. These fat-soluble pigments accumulate selectively in  
1120 neural tissues, including the retina and brain, where they help scavenge reactive oxygen species and  
1121 stabilize cell membranes (Johnson 2014)(Johnson, 2014). Lutein and zeaxanthin, for instance, have  
1122 been associated with improved cognitive performance, especially in domains such as memory,  
1123 processing speed, and visual-spatial function (Yagi et al. 2021) (Lieblein-Boff et al., 2015;  
1124 Vishwanathan et al., 2014). β-carotene, as both an antioxidant and vitamin A precursor, also supports  
1125 immune regulation and neuronal development. Carotenoids are abundant in leafy greens, orange and  
1126 yellow vegetables, corn, and egg yolks. Their absorption is enhanced by dietary fat, and their  
1127 preservation and bioavailability is influenced by cooking techniques, with excessive oxidation during  
1128 high-speed mixing or prolonged exposure to heat shown to degrade carotenoid levels. Research  
1129 shows(Eliášová et al. 2020) that most of the antioxidant anthocyanins in colored-grain wheat are  
1130 destroyed during traditional breadmaking, with retention often dropping below 30%. If processing is  
1131 optimized e.g., sourdough fermentation, high-heat short baking etc this can be reduced. while  
1132 prolonged cooking increases access to lycopene in tomatoes where cell walls need to be broken  
1133 down(Fielding et al. 2005).

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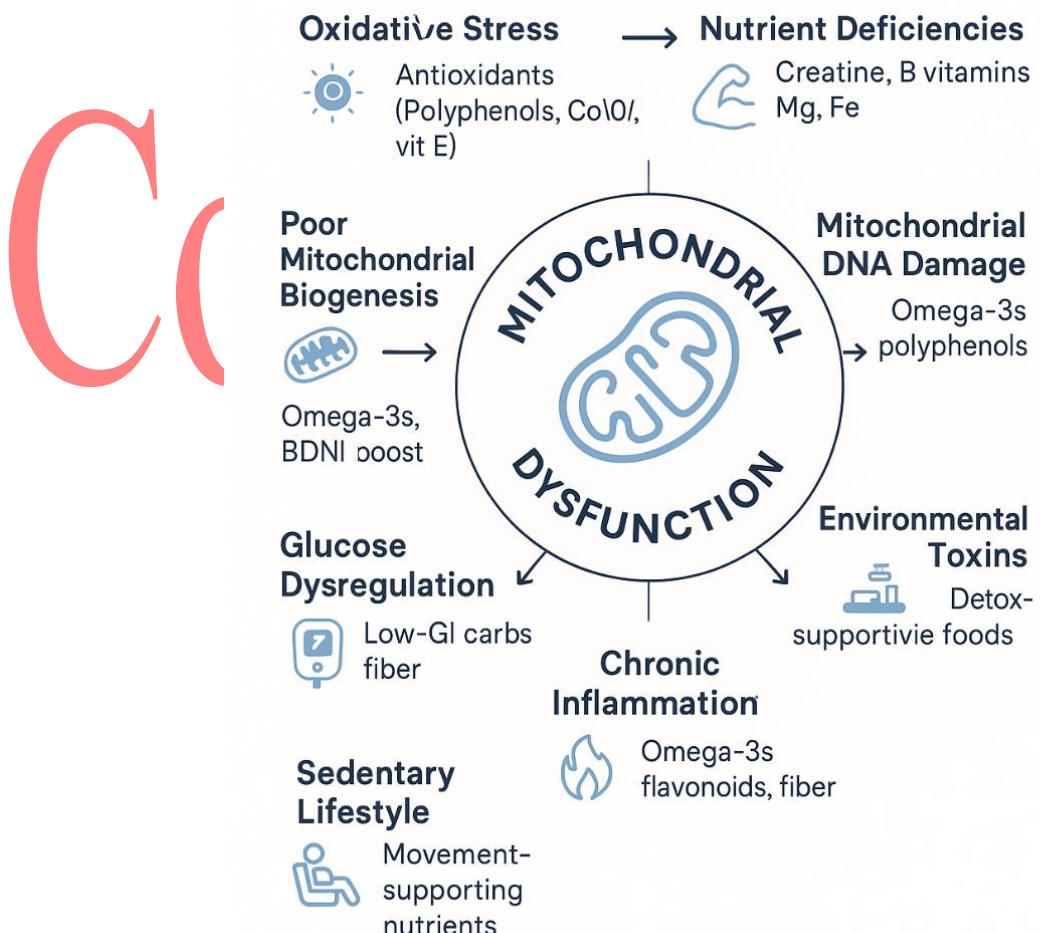
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## 1149 *Mitochondrial Dysfunction*

1150 Mitochondrial dysfunction has been found to be linked to the susceptibility and development of many  
1151 major psychiatric and neurodevelopmental diseases: Alzheimer's(Aran and Singh 2023) Parkinsons  
1152 (Henrich et al. 2023), Major Depressive Disorder (Y. Song et al. 2023), ADHD (Verma et al. 2016)  
1153 (Ogutlu, Kasak, and Tabur 2023) and more limited studies correlating it to ASD (Lombard  
1154 1998)(Khaliulin, Hamoudi, and Amal 2025). Recent studies have shown how mitochondrial  
1155 dysfunction (MD) can lead to dopamine dysregulation, oxidative stress(Wesselink et al. 2019), and  
1156 cognitive impairments, all features of ADHD.  
1157

1158 While little work has been done on connecting ADHD to mitochondrial dysfunction there are  
1159 scientific findings supporting dietary antioxidant treatment of ADHD which accounted for substantial  
1160 alterations in the immune system, epigenetic regulation of gene expression, and oxidative stress  
1161 regulation in ADHD and how immune dysfunction resulting in increased IgE levels might be another  
1162 link between ADHD and allergies(A. Verlaet et al. 2018; Wesselink et al. 2019b)By supplying a  
1163 spectrum of antioxidants (vitamins C and E, polyphenols, carotenoids, omega 3 (discussed above))  
1164 alongside mitochondrial supports (CoQ<sub>10</sub>, lipoic acid, B-vitamins, k2) and trace minerals (selenium,  
1165 zinc, copper), we can potentially increase the protection of neurons, preserve mitochondrial energy  
1166 production, and reduce harmful inflammatory cascades, creating a better basis for optimal cognitive  
1167 and emotional resilience.

## CAUSES OF MITOCHONDRIAL DYSFUNCTION



1168 (1)(1)

1169 Figure 5 – Causes of Mitochondrial dysfunction

1170 Emerging evidence connecting mitochondria with behavioural outcomes.

- **Animal models:** Impaired mitochondrial function in the nucleus accumbens has been shown to reduce social dominance behaviours in mice (Zalachoras et al. 2022) Strikingly, supplementation with nicotinamide, a dietary precursor to NAD<sup>+</sup>, restored mitochondrial efficiency and reversed these behavioural deficits in an anxiety-expressing mouse model (Hollis et al. 2015). This suggests that mitochondrial bioenergetics are not only mechanistically linked to behaviour, but also potentially reversible through targeted nutritional support.
- **Human data:** Large-scale analyses reinforce this connection. Using *UK Biobank* data, (Liu et al. 2023) identified significant associations between mitochondrial DNA variants (mtSNPs) and anxiety phenotypes, including elevated GAD-7 scores and self-reported anxiety. Importantly, these effects were amplified in the presence of systemic inflammation (C-reactive protein), indicating a mitochondria–immune–linked behaviour t

1183

1184 ***ATP for Mitochondrial Energy***

1185 Adenosine Triphosphate (ATP) is the primary energy carrier in all cells and is crucial for maintaining  
1186 normal cellular function **ATP production** decreases as a result of mitochondrial dysfunction. **ATP**  
1187 **markers from are associated with better global cognitive performance (MoCA scores)** in  
1188 healthy older adults (Lopez et al. 2023). In individuals with ADHD, mitochondrial  
1189 dysfunction can lead to reduced ATP production, neurochemical imbalances, oxidative stress which  
1190 impacts brain energy metabolism, cognition and attention (Ogutlu, Kasak, and Tabur 2023; Walther  
1191 et al. 2023)..

1192 Nicotinamide adenine dinucleotide (NAD<sup>+</sup>) is a central coenzyme in oxidative phosphorylation,  
1193 acting as an electron carrier that enables ATP generation. Incorporating **NAD<sup>+</sup> precursors** into the  
1194 BRAIN Diet reinforces mitochondrial energy metabolism, particularly in contexts of deficiency.  
1195 Patients with adult-onset mitochondrial myopathy, niacin supplementation (750–1,000 mg/day)  
1196 successfully restored blood and muscle NAD<sup>+</sup> levels, up to eightfold, and improved mitochondrial  
1197 biogenesis and muscle performance (Pirinen et al. 2020) underscoring niacin's potential as an  
1198 effective dietary intervention for enhancing mitochondrial function.

1199 Incorporating NAD<sup>+</sup> precursors into the BRAIN Diet—such as niacin (vitamin B<sub>3</sub>), nicotinamide  
1200 riboside, or tryptophan—can reinforce mitochondrial energy metabolism, particularly in states of  
1201 deficiency. In patients with adult-onset mitochondrial myopathy, high-dose niacin supplementation  
1202 (750–1,000 mg/day) restored blood and muscle NAD<sup>+</sup> levels by up to eightfold, improved  
1203 mitochondrial biogenesis, and enhanced muscle performance (Pirinen et al., 2020). By sustaining  
1204 NAD<sup>+</sup> availability, mitochondrial ATP production remains efficient, supporting the neuronal energy  
1205 demands required for sustained attention, motivation, and goal-directed behavior.

1206 These findings reinforce the importance of nutrient strategies within the BRAIN  
1207 Diet that support NAD<sup>+</sup> availability, glutathione synthesis, and mitochondrial  
1208 health—such as **niacin-rich foods** (e.g., salmon, chicken breast, turkey, peanuts,  
1209 and mushrooms), **sulphur-containing vegetables** that provide glutathione  
1210 precursors (e.g., broccoli, Brussels sprouts, garlic, onions), and **polyphenol-rich**

1211 sources (e.g., blueberries, green tea, dark chocolate, extra virgin olive oil)—to  
1212 sustain motivation, resilience, and cognitive performance.

1213

1214 **Table X. Dietary Sources of NAD<sup>+</sup> Precursors in the BRAIN Diet**

NAD <sup>+</sup> Precursor	Role in NAD <sup>+</sup> Metabolism	Key BRAIN Diet Food Sources
<b>Niacin (Vitamin B<sub>3</sub>)</b>	Directly converted to NAD <sup>+</sup> via salvage pathway	Chicken, turkey, tuna, salmon, mushrooms, peanuts, whole grains
<b>Nicotinamide Riboside</b>	Efficient NAD <sup>+</sup> precursor with neuroprotective potential	Dairy milk, whey protein, yeast-containing foods (e.g., sourdough bread)
<b>Tryptophan</b>	Converted to NAD <sup>+</sup> via kynurenine pathway	Turkey, chicken, eggs, pumpkin seeds, oats, soybeans
<b>Nicotinamide Mononucleotide (NMN)</b>	Direct NAD <sup>+</sup> intermediate in salvage pathway	Edamame, broccoli, cucumber, avocado
<b>Polyphenols (e.g., resveratrol)</b>	Activate SIRT1, enhancing NAD <sup>+</sup> -dependent processes	Grapes, blueberries, cranberries, peanuts, dark chocolate

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1216

### *Inflammation and ROS*

1217 When the amount of anti-oxidants generated is inadequate to offset the detrimental effects of  
1218 hazardous **reactive oxygen species ROS**, oxidative stress arises. Increased oxidative stress has been  
1219 linked to cellular damage, DNA repair system malfunction, and in turn **mitochondrial dysfunction**  
1220 (MD)(Solleiro-Villavicencio and Rivas-Arancibia 2018a).

1221 High levels of can cause astrocytes and microglia to become activated; reactive astrocytes can release  
1222 pro-inflammatory cytokines (e.g.,ADHD associated biomarkers IL-6, IL-1 $\beta$ , TNF- $\alpha$  (Chang et al.  
1223 2020a)), exacerbating inflammation and neuronal damage creating a vicious cycle (Solleiro-  
1224 Villavicencio and Rivas-Arancibia 2018b) This vicious circle may increase the risk of ADHD  
1225 pathogenesis. Also, increased H<sub>2</sub>O<sub>2</sub> due to MD may play a functional role in ADHD by suppressing  
1226 dopamine release in the striatum pathway. This may be one of the possible mechanisms underlying  
1227 dopamine deficiency in the frontostriatal pathway in ADHD.

1228

1229 **Glutathione (GSH)** is one of the body's major antioxidants. Low levels may suggest oxidative  
1230 stress,; elevated GSH levels which have been recorded against ADHD subjects may also reflect a  
1231 **compensatory response** to increased oxidative stress (Verlaet et al. 2019). Furthermore,  
1232 mitochondrial metabolism of lactate depends on GSH for ROS neutralization, optimizing  
1233 mitochondrial energy use.

1234

### *Other key antioxidants*

1235 Many other studies have been carried out looking at antioxidant agentsas modulators of  
1236 mitochondrial function(Vásquez-Reyes et al. 2021) and antioxidants such as quercetin showing  
1237 efficacy in reducing oxidative stress and related improvements in symptoms for ADHD and ASD

1238 symptoms, (Boots, Haenen, and Bast 2008), potentially due to quercetin's link to enhancing  
1239 mitochondrial baseline activity and energy production(Davis et al. 2009).  
1240

1241 **Quercetin** is an effective antioxidant agent which scavenges ROS(Boots, Haenen, and Bast 2008) and  
1242 has antioxidant, anti-inflammatory, and anti-neuroinflammatory and neuroprotective  
1243 properties(Tongjaroenbuangam et al. 2011). Isoquercetin (glycosylated quercetin) is more completely  
1244 absorbed than quercetin in the aglycone form, and that the simultaneous ingestion of quercetin with  
1245 vitamin C, folate and additional flavonoids improves bioavailability(Y. Li et al. 2016). Also studies  
1246 have shown quercetin bound to a sugar molecule forming quercitrin has anti-inflammatory and anti-  
1247 oxidative effects may be augmented by the co-ingestion of N-3 polyunsaturated fatty acids and olive  
1248 oil (Camuesco et al. 2006).

1249 The estimated flavonoid intake ranges from 50 to 800 mg/day (About 75% of dietary polyphenol  
1250 count is quercetin(Y. Li et al. 2016)). It is abundant in capers (Neveu V et al database 2010), apples ,  
1251 onions, berries, kale and soybeans.

1252 **Genistein** a soy-derived isoflavonoid, has shown potential as a modulator of several biochemical  
1253 pathways, including the endocannabinoid system and neuroinflammation (Fuloria et al. 2022),  
1254 potentially enhancing the activity of certain endocannabinoids like anandamide (Thors, Eriksson, and  
1255 Fowler 2007). It has been confirmed to have the ability to alleviate the deleterious effects of  
1256 oxidative stress on neuronal injury, such as preventing neuronal death, increasing the production of  
1257 hippocampal glutathione (GSH) and superoxide dismutase (SOD), and lowering lipid peroxidation,  
1258 ROS, and nitric oxide production. Since genistein is believed to pass the blood–brain barrier to exert  
1259 its neuroprotective effect, it is extensively applied in the investigation of the treatment of  
1260 neurodegenerative diseases, such as Alzheimer's and Huntington's(Fuloria et al. 2022).

1261  
1262 **Coenzyme (CoQ10)**: This antioxidant and energy production cofactor has been associated with  
1263 ADHD and levels may be improved through supplementation(Mantle and Hargreaves 2024). CoQ10  
1264 deficiency leads to reduced ATP production and mitochondrial dysfunction, which may contribute to  
1265 the neurocognitive issues in ADHD (Szulc et al., 2018) . The decline in presence of CoQ10 in  
1266 humans with age; is dramatic with over 50% depletion between 20 years of life and 60 years which  
1267 also relates to dietary levels in animal organ meats which are the number one dietary source. Low  
1268 levels of the coenzyme B6 can cause dysfunctions, prior to the formation of vitamin Q10, to  
1269 DNA(Pravst, Zmitek, and Zmitek 2010). Organ meats are the highest source at upto 12mg per 100g,  
1270 with olive oil being the the highest plant source though at .06- 2mg per 100g it is not possible to  
1271 match therapeutic level doses. With great variations between producers and harvest time having been  
1272 noted , total CoQ dropped by 53%-56% between three weeks of the harvesting of two brands  
1273 (Zmitek, Rodríguez-Aguilera, and Pravst 2014; Deichmann, Lavie, and Andrews 2010).  
1274

## 1275 **Key Compounds Supporting Mitochondrial Function**

1276 Several amino acid–derived nutrients and other cofactors are integral to sustaining mitochondrial  
1277 energy production, buffering oxidative stress, and preserving neuronal function. These compounds  
1278 often originate from dietary proteins but exert systemic effects beyond neurotransmitter synthesis.  
1279 Evidence suggests they may mitigate mitochondrial dysfunction, a feature common to ADHD,

1280 depression, and neurodegenerative conditions. Omnivore diets naturally supply creatine, taurine, and  
1281 carnosine, which may support mitochondrial and neuroprotective functions; vegan diets rely on  
1282 endogenous synthesis.

Compound	Primary Function(s)	Key Evidence
Creatine	ATP recycling via the phosphocreatine system; supports high-energy demand in neurons	Supplementation improves cognitive performance in sleep-deprived adults (McMorris et al., 2007) and enhances mitochondrial energy buffering in neurodegenerative models (Andres et al., 2008).
Taurine	Osmoregulation, calcium handling, GABA modulation, mitochondrial membrane stabilisation	Taurine protects mitochondrial function under oxidative stress in neuronal cultures (Ripps & Shen, 2012) and modulates neuroinflammation.
Carnitine	Transports long-chain fatty acids into mitochondria for $\beta$ -oxidation	Acetyl-L-carnitine improves mitochondrial bioenergetics and reduces depressive symptoms in RCTs (Nasca et al., 2018).
CoQ10	Electron transport chain cofactor; lipid-soluble antioxidant	CoQ10 supplementation improves mitochondrial efficiency and reduces oxidative stress markers in neurological disorders (Hernández-Camacho et al., 2018).
Carnosine	Antioxidant and pH buffer; protects mitochondrial enzymes from glycation	Carnosine has been shown to reduce oxidative damage and preserve mitochondrial enzyme activity in ageing models
Riboflavin (B2)	Involved in mitochondrial oxidative metabolism, riboflavin supports the electron transport chain.	Deficiency results in impaired fat and amino acid oxidation, impacting ATP production and energy metabolism (Martínez et al., 2015).

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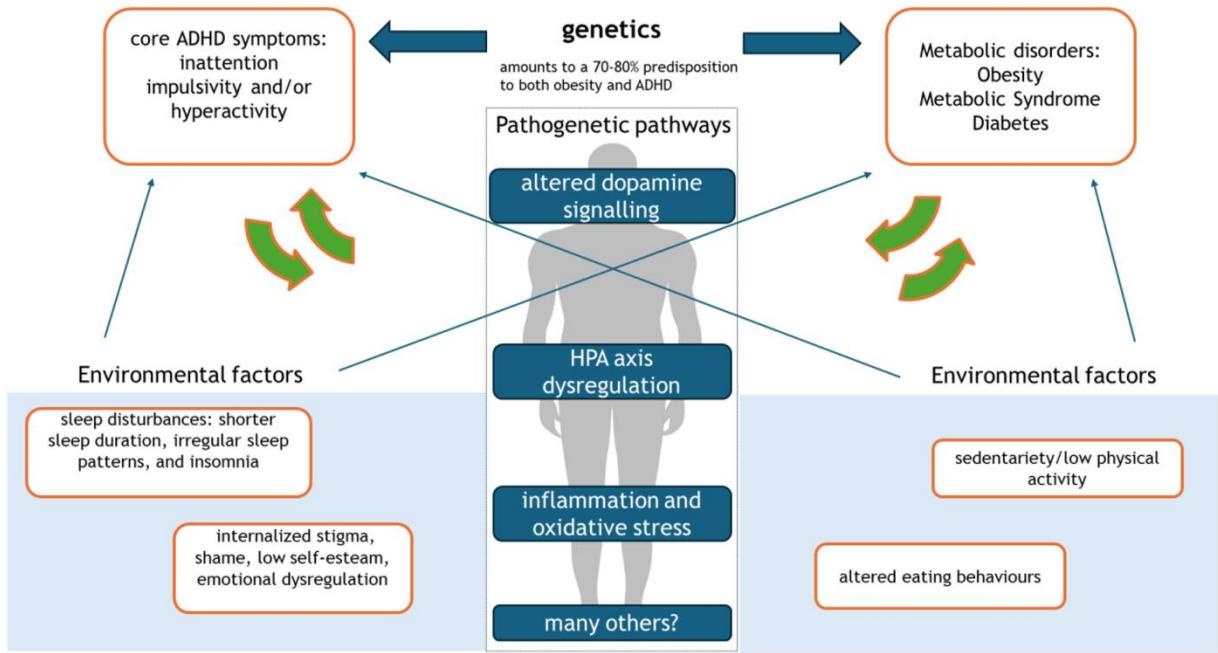
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1301 Figure 6 - Overlapping pathogenetic pathways between metabolic disorders and ADHD

1302 *Interconnected Dysregulation: Appetite, Inflammation, and Energy*

1303 ADHD is marked by multi-system dysregulation, extending beyond neurotransmission to include  
 1304 appetite, circadian rhythm, inflammation, and energy regulation. These systems are deeply  
 1305 interdependent, dysfunction in one domain amplifies dysfunction in others. For example, fatigue-  
 1306 induced sugar cravings may temporarily compensate for low dopamine or energy, but over time  
 1307 exacerbate insulin resistance and systemic inflammation. In turn, chronic inflammation can spill into  
 1308 the brain (neuroinflammation), impairing neurotransmitter synthesis and contributing towards  
 1309 mitochondrial dysfunction. Simultaneously, gut dysbiosis driven by poor food choices further  
 1310 disrupts neurotransmitter support and immune signaling, while impaired glucose and insulin control  
 1311 fuels additional metabolic and cognitive instability. This feedback loop of dysregulation highlights  
 1312 the need for dietary frameworks, such as the BRAIN Diet, that address all these challenges in  
 1313 concert.

1314

1315 *Metabolic Syndrome and the Need for Dietary Integration*

1316 Insulin resistance is a hallmark of metabolic syndrome, which elevates the risk for cardiovascular  
 1317 disease, central obesity, and type 2 diabetes. Individuals with ADHD show a significantly higher risk  
 1318 of developing metabolic syndrome (Engström et al. 2003) reinforcing the need to address metabolic  
 1319 health within any brain-focused dietary approach.

1320 *Glucose Metabolism and ADHD*

1321  
1322 The brain relies heavily on glucose for energy. Poor glucose regulation, such as in hypoglycemia or  
1323 glucose intolerance, can impair cognitive function and worsen ADHD symptoms, including difficulty  
1324 concentrating and mood instability. Studies have found individuals with ADHD may have altered  
1325 glucose uptake in brain regions involved in attention and impulse control in both inattentive and  
1326 hyperactive children(Zametkin et al. 1990).

1327  
1328 (Zelicha et al. 2022) The Green Mediterranean Diet study produced greater visceral adipose tissue  
1329 (VAT) loss than MED or control ( $\approx -14.1\%$  vs  $-6.0\%$  vs  $-4.2\%$ ); VAT loss tracked with higher total  
1330 plasma polyphenols and with the microbiome-derived markers urolithin A (via ellagitannins:  
1331 walnuts/pomegranate) and hippuric acid Green tea catechins (e.g., EGCG, EGC) (. Proteomics  
1332 suggest VAT reduction is accompanied by shifts in adiposity-related pathways. Parallel analyses  
1333 (Pachter et al. 2024) showed MED/green-MED attenuated brain atrophy by  $\sim 50\%$ , with glycemic  
1334 control contributing to the neuroprotective signal—consistent with a polyphenol–fiber–microbiome  
1335 synergy improving metabolic and brain aging phenotypes.

1336  
1337 In ADHD, inefficient glucose metabolism or insulin resistance may increase lactate levels, while  
1338 lactate can fuel the brain during periods of high demand, excessive lactate levels can contribute to  
1339 neuronal dysfunction leading to cognitive deficits, mental fatigue, and attention difficulties.

1340 ***PPAR/RXR and metabolic health and brain function***

1341 The regulation of adipose tissue by nuclear receptors such as PPAR- $\alpha$  and PPAR- $\gamma$  plays a central  
1342 role in the interplay between metabolic health and brain function, an axis increasingly implicated in  
1343 ADHD. Adipose tissue expresses a suite of genes involved in lipid metabolism, insulin sensitivity  
1344 and inflammation , all of which are under the transcriptional control of PPARs(Marx et al. 2004).  
1345 Omega-3 fatty acids serve as partial agonists for both PPAR- $\alpha$  (which promotes fatty acid oxidation  
1346 and mitochondrial efficiency) and PPAR- $\gamma$  (which regulates adipocyte differentiation and anti-  
1347 inflammatory adipokine release). Activation of these receptors by EPA and DHA improves insulin  
1348 signaling and suppresses pro-inflammatory cytokine expression, shifting adipose tissue toward a  
1349 metabolically protective phenotype.

1350 Inflammation originating from dysfunctional adipose is known to cross the blood–brain barrier and  
1351 disrupt neural signaling. Through its emphasis on anti-inflammatory and insulin-sensitizing foods,  
1352 the BRAIN Diet seeks to restore adipose metabolic flexibility, lower peripheral cytokine load, and  
1353 reduce neuroinflammation, thereby creating a more favorable neuroimmune environment for  
1354 cognitive stability, dopamine regulation, and long-term attentional control. By also incorporating  
1355 nutrients such as magnesium(Cazzola et al. 2024), polyphenols (e.g., quercetin, resveratrol), B  
1356 vitamins, and short-chain fatty acids (e.g., from prebiotic fiber), the diet aims to improve  
1357 mitochondrial biogenesis and lipid oxidation in white adipose tissue, particularly visceral fat, which  
1358 is a key source of low-grade systemic inflammation. EPA and DHA may also enhance gut  
1359 microbiome diversity and reduce neuroinflammatory cytokines like IL-6 and TNF- $\alpha$ , supporting both  
1360 brain and gut health (Chang et al. 2020a) (Zinkow et al. 2024).

1361 DHA-induced PPAR $\gamma$ -RXR $\alpha$  activation has been shown to enhance synaptic remodeling, neuronal  
1362 survival, and cognitive resilience (Majou and Dermenghem 2024) , supporting its mechanistic  
1363 relevance in neurodevelopmental disorders such as ADHD. Additionally, PPAR activation mediates  
1364 mitochondrial biogenesis and lipid handling in astrocytes and microglia, reinforcing omega-3's role  
1365 in sustaining neuroenergetic stability and long-term cognitive health(Corona and Duchen 2016).

1367 ***HPA Axis, ANS Dysregulation, and Their Role in Metabolic and ADHD Symptoms***

1368 The hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS) are central  
 1369 regulators of the body's response to stress. Dysregulation in either system is increasingly recognized  
 1370 in ADHD and contributes not only to emotional dysregulation and cognitive dysfunction, but also to  
 1371 metabolic imbalances such as insulin resistance and disrupted appetite signaling.

1372 Research shows that children and adults with ADHD often display an abnormal cortisol rhythm or a  
 1373 blunted cortisol awakening response (Isaksson et al. 2012; Chang et al. 2020b; Jue et al. 2023).  
 1374 Genetic studies support this with polymorphisms in HPA-related genes like NR3C1(Fortier et al.  
 1375 2013; Carpene et al. 2022) (Fortier et al., 2013; Carpene et al., 2022) These hormonal irregularities  
 1376 may reduce resilience to stress and increase susceptibility to impulsivity, anxiety, and poor decision-  
 1377 making.

1378 HPA axis dysfunction also influences neurotrophins like BDNF(Ziae et al. 2024), which may either  
 1379 increase (as a compensatory response to chronic low cortisol) or decrease (especially in inattentive  
 1380 subtypes), affecting neuroplasticity and synaptic development(S.-J. Tsai 2003; 2017).

1381 Meanwhile, ANS dysfunction in ADHD, marked by low parasympathetic tone and high sympathetic  
 1382 dominance, can manifest as poor heart rate variability, heightened reactivity, and disrupted  
 1383 sleep(French et al. 2023). These patterns promote increased cravings, poor glucose regulation, and  
 1384 disrupted leptin and ghrelin signaling, leading to unhealthy eating behaviors and weight gain with the  
 1385 potential for escalating into more serious metabolic disorders (Spiegel, Leproult, and Van Cauter  
 1386 1999), (Benedict et al. 2011).

1387 While targeted nutrition can do much to counteract stress, stabilize energy and influence  
 1388 neurotransmitter levels, it is not always best to eat just to spike neurotransmitters. It is critical to  
 1389 recognize when fatigue is better addressed through non-dietary interventions. Light physical activity  
 1390 (e.g., a brisk 10-minute walk) and mindful breathwork can activate the dopaminergic and  
 1391 parasympathetic systems, respectively, improving mood and reducing stress-induced cravings,

1392 With combinations of lifestyle and dietary interventions these systems can be brought back towards  
 1393 balance:

- 1394 • Sleep hygiene - supports cortisol regulation and reduces sympathetic dominance ((Checa-Ros  
 1395 et al. 2023); (Michael R Lyon 1, n.d.)).
- 1396 • Moderate physical activity (see below) - improves parasympathetic tone, stabilizes glucose  
 1397 metabolism, and modulates adenosine and dopamine pathways (Ratey and Loehr 2011)
- 1398 • Mindful eating and stress-reduction practices reduce cortisol and improve appetite regulation  
 1399 (Torske et al. 2024; Katterman et al. 2014)(Torske et al., 2024; Katterman et al., 2014).
- 1400 • Complementary dietary approaches - Fast mimicking diet(Rangan et al. 2022), Time  
 1401 restricted Feedinghas been shown to reduce insulin sensitivity (Sutton et al. 2018) , high  
 1402 polyphenols have been shown to reduce viseral adiposity, see above (Zelicha et al. 2022).
  - 1403     ○ Note: Fasting has been shown to increase cortisol which can stimulate appetite, alter  
 1404 mood and memory and alter peripheral metabolism in favor of weight gain(Nakamura,  
 1405 Walker, and Ikuta 2016), so fasting should be carefully observed for those with high  
 1406 cortisol and stress. With ADHD there is often a sensitivity to stress responses seeing  
 1407 many increased negative biological and psychological affects be it, inflammation,

- 1408 degraded immune response, poor digestion, anxiety, depression, or heightened  
 1409 emotional reactivity and diminished coping capacity .  
 1410 • Specific dietary compounds - taurine and adenosine-regulating nutrients (e.g., green tea  
 1411 polyphenols, plant-based methyl donors i.e. folate, choline, betaine) offer dietary leverage  
 1412 points for modulating the HPA axis and restoring neurotransmitter balance (Md. Jakarta a,  
 1413 n.d.) (Q. Jia et al. 2024)

1414 **Adenosine:** Adenosine is a critical regulator of dopamine signaling, sleep, inflammation, and neural  
 1415 plasticity, all of which are closely tied to ADHD symptoms. It is typically generated from the  
 1416 breakdown of ATP which increases during the day creating sleep ‘pressure’. Imbalances in adenosine  
 1417 signaling can contribute to symptoms of ADHD (Valladão et al. 2024), such as inattention and  
 1418 hyperactivity.

1419 **Taurine** is a sulfur-containing, semi-essential amino acid that occurs naturally in the body. It plays a  
 1420 protective role in modulating inflammation and oxidative stress in various disease models. Studies  
 1421 (Md. Jakarta a, n.d.) indicate that taurine may prevent neurotoxicity, stabilize neurotransmitter  
 1422 balance, and support cognitive health. It also exhibits adaptogenic properties by buffering the brain  
 1423 against chronic stress and regulating the hypothalamic-pituitary-adrenal (HPA) axis, including the  
 1424 reduction of cortisol levels. There have been studies in rat ADHD models showing positive  
 1425 improvements for attention and hyperactivity but not in-human. Meats and shell fish can provide  
 1426 it direct or foods containing precursor cysteine (Wójcik et al. 2010)

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## 9. -Aligned Foods & Metabolic Regulators (Stress, Fasting, Chrono-Nutrition,)

- **Best foods for morning vs. evening** (protein vs. complex carbs for energy)
- **Carb timing for ADHD energy regulation**
- **Melatonin precursors & night-time foods** (cherries, pistachios, tart cherry juice)
- **Caffeine, circadian rhythms, & ADHD focus**
- **Exercise**

1436 Aligning nutrient intake with circadian and activity rhythms represents a precision-based upgrade to  
 1437 static dietary planning. Also in light of many medications, particularly amphetamines, a blunting of  
 1438 the appetite is experienced, therefore nutrient loaded for breakfast is even more important (Nancy  
 1439 Clark 2022).

1440 We discussed above how nutritional strategies can determine which amino acids are encouraged to  
 1441 cross the BBB, but beyond that it has to be considered which foods and drinks are taken at what  
 1442 times of the day in keeping with circadian rhythms.

1443 Nutritional Timing and Fasting

1444

Phase	Dopamine	Norepinephrine	GABA	Key Strategy
<b>Morning</b> (Task initiation)	⬆ Boost synthesis for	⬆ Supports alertness, working memory	⬇ Still low to allow activation	• High-tyrosine protein (eggs, tofu, turkey) • B6, iron, vitamin C

Phase	Dopamine motivation & focus	Norepinephrine	GABA	Key Strategy
<b>Midday</b> (Sustain cognition & emotion)	— Maintain steady release	— Regulate attention, prevent fatigue	↑ Light GABA tone helps reduce overstimulation	Limit sugar and processed carbs • Complex carbs + protein • Magnesium, zinc, B-complex • Leafy greens, seeds, legumes
<b>Afternoon</b> (Prevent crashes, emotional reactivity)	⬇ Gentle taper	— Avoid overstimulation	↑ Increased GABA tone aids emotional balance	• Omega-3s, antioxidants Polyphenols (berries, cocoa) • Avoid caffeine, simple sugars
<b>Evening</b> (Wind-down, sleep prep)	⬇ Suppress for calm	⬇ Lower arousal	↑ Strong GABA activation for sleep onset	• Tryptophan + complex carbs (pumpkin seeds + oats) • Magnesium, taurine, L-theanine Herbal teas (e.g. chamomile, lemon balm)

1445

Table 8 - Circadian support of Neurotransmitters.

1446

**Exercise-aligned nutritional timing** should be an integral component of all ADHD dietary plans. Physical activity triggers a cascade of neurochemical and metabolic shifts that enhance the brain's receptivity to specific nutrients, particularly those involved in neurotransmitter synthesis, mitochondrial function, and neuroplasticity. For example, post-exercise windows offer heightened sensitivity to glucose and amino acids, making it an ideal time to deliver precursors like tyrosine (dopamine), tryptophan (serotonin), magnesium, and omega-3s to support recovery and cognitive resilience. Moreover, exercise-induced BDNF surges can be potentiated by polyphenols(Davis et al. 2009) , DHA, and curcumin consumed within this window, suggesting a synergistic opportunity to enhance mood and learning consolidation.

1447

Physical activity, when aligned with circadian timing, not only entrains peripheral clocks but also enhances neuroplasticity, BDNF secretion, and mitochondrial efficiency , all of which are core to the BRAIN diet's objectives. Strategic timing of exercise may therefore amplify the cognitive and metabolic benefits of the dietary protocol, particularly in populations with circadian disruption such as ADHD.

1448

### 1449 **Exercise: Enhancing Neuroplasticity and Nutrient Synergy**

1450

Physical activity plays a crucial role in any ADHD dietary strategy, not only for its well-established benefits on mood and focus but also for how it shapes the body's metabolic and neurochemical environment. Exercise induces a cascade of physiological changes, such as increased blood flow, elevated BDNF (Brain-Derived Neurotrophic Factor), improved insulin sensitivity, and enhanced mitochondrial activity, that temporarily heighten the brain's receptivity to key nutrients.

1451

These post-exercise windows present an optimal time to deliver nutrients critical to neurotransmitter synthesis and brain recovery. For example, amino acids like tyrosine and tryptophan, essential for

1468 dopamine and serotonin production respectively, are more efficiently utilized after physical exertion.  
1469 Similarly, magnesium, omega-3 fatty acids, and B-vitamins—which support ATP production and  
1470 neuronal signaling—can have amplified effects when timed alongside or following activity.

1471 Moreover, exercise-induced BDNF surges can be synergistically potentiated by polyphenols (e.g.,  
1472 blueberries, green tea, *Davis et al., 2009*), DHA, and curcumin, all of which may enhance learning  
1473 consolidation, synaptic growth, and emotional regulation. These interactions highlight the value of  
1474 *nutrition-exercise coupling* as an underused therapeutic lever in ADHD management.

1475 Timing also matters. Physical activity early in the day helps align circadian rhythms, regulate cortisol  
1476 release, and entrain peripheral clocks, supporting improved sleep, appetite regulation, and metabolic  
1477 stability—all frequently disrupted in ADHD. This makes circadian-aligned exercise not only a  
1478 metabolic tool, but a core component of the BRAIN diet’s strategy to restore homeostasis in  
1479 neurodivergent populations.

1480

### 1481 ***Neurochemical Rhythms and Chrono-Nutrition***

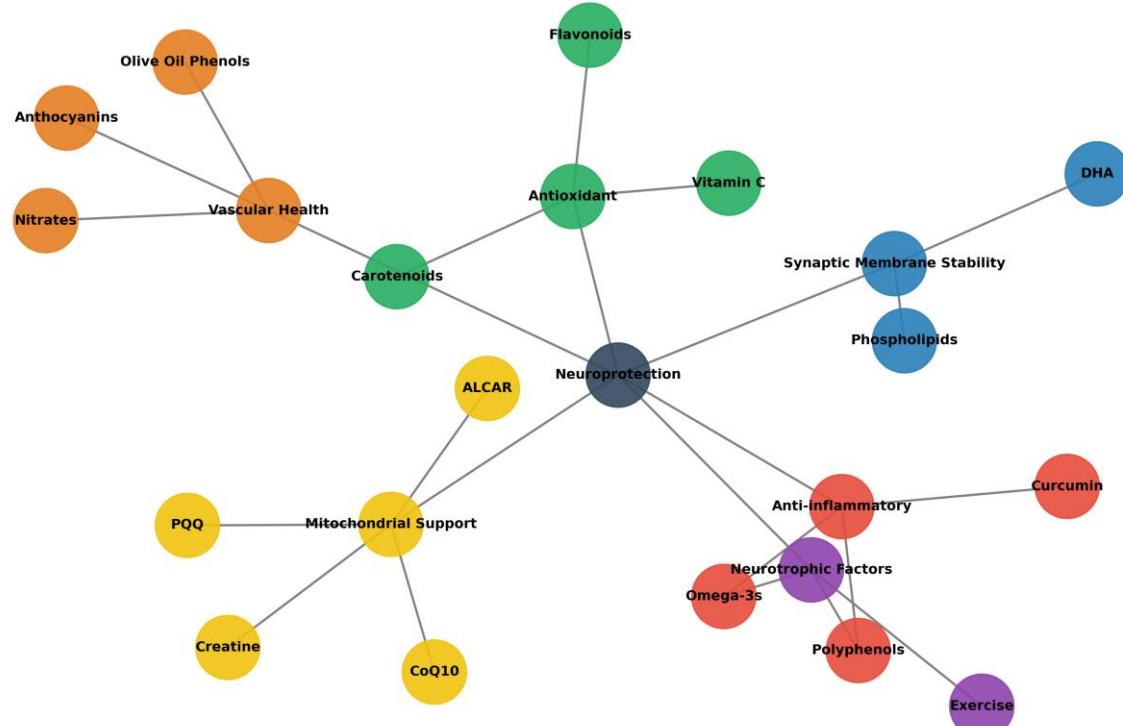
1482  
1483 Neurotransmitter activity follows circadian rhythms that may influence how the brain responds to  
1484 specific nutrients throughout the day. Dopamine and cortisol tend to peak in the morning,  
1485 supporting alertness and goal-directed behaviour, while serotonin and melatonin rise toward the  
1486 evening, modulating mood, impulse control, and sleep. Aligning nutrient intake with these natural  
1487 rhythms - such as prioritising tyrosine- and phenylalanine-rich foods earlier in the day, and  
1488 tryptophan-rich, carbohydrate-supported meals later on - may enhance neurochemical synthesis  
1489 and receptor sensitivity. This chrono-nutritional approach offers an additional lens through which  
1490 to personalise dietary strategies for cognitive regulation, especially in neurodevelopmental  
1491 conditions like ADHD.

1492

### 1493 **10. Neuroprotective Herbal & Functional Foods**

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1495 The herbal and functional foods are the final pillar in our neuroprotective and brain health diet.  
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### Neuroprotection Pathways in the BRAIN Diet



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## *Culinary vs. Therapeutic Use of Herbs and Spices*

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**Contingual**  
Initial clinical trials that test the diet should emphasize the use of herbs and spices in culinary amounts, those typically found in traditional cuisines, rather than the high-dose medicinal levels often used in isolated clinical research. The core efficacy of the BRAIN Diet must rest on its integrated framework of precision dietary strategies, nutrient density, and food matrix interactions, rather than any one concentrated intervention. That said, future trials should explore therapeutic levels of specific spices or adaptogens (e.g. curcumin, saffron, gingerols) where targeted modulation of dysregulated biological systems is warranted.

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## *Food synergies with spices for targeting dysregulated systems*

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There will be moments when individuals experience serious dysregulation in one biologic system, or more, and when the diet could be used to target certain systems or pathways i.e. increasing the inflammatory dietary targets such as certain spices, higher omega 3 and polyphenol combinations. In such instances raising targeted active ingredients towards therapeutic levels might be beneficial if a medication model is not desired. Many spices have been used in clinical trials against the core bio systems dysregulation that the BRAIN diets targets and many members of the Zingiberaceae family (which includes ginger, turmeric, and galangal) have pleiotropic effects overlapping between metabolic regulation and neurocognitive outcomes. By reducing inflammation and oxidative stress, these herbs and spices can modulate neurotransmitter production, improve mitochondrial function, potentially improving reducing anxiety, and improving cognitive performance.

<b>Herb/Spice</b>	<b>Primary Indication</b>	<b>Typical Dose/Form</b>	<b>Reference / Study Source</b>
Saffron	ADHD symptoms, mood regulation	30 mg/day standardized extract (stigmas)	(Jackson et al. 2021; Lopresti and Drummond 2014)
Curcumin (Turmeric)	Anti-inflammatory, neuroprotective	500–1000 mg/day curcumin with piperine	Goozee et al., 2016; Rainey-Smith et al., 2022
Ginger	Gut-brain axis support, anti-inflammatory	1–2 g/day fresh or powdered root	Mashhadi et al., 2013; Sahebkar, 2013
Cinnamon	Glycemic control, insulin sensitivity, cognition	1–3 g/day cassia or Ceylon cinnamon powder	Anderson et al., 2004; Khan et al., 2003
Peppermint	Mental clarity, alertness	Herbal tea; essential oil inhalation	Moss et al., 2008; Kennedy et al., 2011
Sage	Memory and cognitive enhancement	200–400 mg/day extract or culinary doses	Tildesley et al., 2003; Kennedy et al., 2006
Rosemary	Focus, antioxidant, neuroprotective effects	Fresh herb or 250–500 mg/day extract	Pengelly et al., 2012; Moss & Oliver, 2012

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1521 **Saffron** - (it's thought to boost serotonin and have antioxidant crocin and it has shown promising  
 1522 effects on depression(Lopresti and Drummond 2014), mood, cognition(Jackson et al. 2021), and  
 1523 ADHD symptoms at doses around 30 mg/day of standardized extract ((Baziar et al. 2019)). While  
 1524 its distinct flavour and limited culinary uses make it impractical for routine dietary inclusion, it  
 1525 represents a compelling bioactive for future trials and adjunctive supplementation in neuro-  
 1526 supportive protocols. The delicate oils contained in saffron such as

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1528 **Curcumin** - Systematic reviews affirm that curcumin supplementation can improve memory  
1529 performance in older adults and enhance overall cognitive function in both healthy and at-risk  
1530 populations . However, curcumin's benefits may depend on  
1531 formulation due to its poor natural bioavailability

1532 ***When to Seek Medical Advice***

1533 Any significant dietary changes or use of high-dose supplements should be made in consultation with  
1534 a qualified healthcare professional.

1535

1536 ***Herbals and medication interactions***

1537  
1538 While culinary use of herbs and spices is generally safe, therapeutic doses may have potent biological  
1539 effects and could interact with medications or underlying conditions.

1540

1541 ***Functional Foods***

1542 The target spices above, the polyphenols, the foods with good amino acid ratios, the friendly gut  
1543 bacteria producing foods all form part of the functional food profile of the diet. Functional foods are  
1544 broadly defined as “foods that provide health benefits beyond basic nutrition,” often by improving  
1545 physiological functions or reducing disease risk. This includes naturally occurring foods like fatty  
1546 fish or fermented dairy, as well as foods enhanced through modern innovation, such as sprouted  
1547 grains, UV-grown mushrooms, or microencapsulated omega-3 oils. The FUFOSE (Functional Food  
1548 Science in Europe) model laid early groundwork for this definition. However, the food's functional  
1549 impact often depends upon it's own matrix of physical structures and its components, it's preparation  
1550 and deliver system if it is processed(Yu et al. 2023) and the interactions between different foods  
1551 consumed together, and how these collective effects influence digestion, absorption, metabolism, and  
1552 ultimately physiological function.

1553 The BRAIN Diet embraces the functional food philosophy but deliberately moves away from  
1554 reductionist interpretations that isolate nutrients from the broader biological and food matrix context.  
1555 As we have highlight above omega 3 needs to bind to the correct phospholypids tryptophan will  
1556 compete with other LEAAs unless carbohydrates create an insulin spike, turmeric is not just a  
1557 curcumin supplement, it's part of a culinary matrix that includes fats which with heat, can increase  
1558 enhance curcumin's absorption.

1559

1560 ***Summary and Perspectives***

1561 This review paper comes at a prescient moment, when nutritional science is evolving rapidly.  
1562 We must now move toward a position where key precision nutrition facts are not only  
1563 published but also socialised into public knowledge and practice. This dietary program and  
1564 corpus of integrated science must now be further developed, also in support of other dietary  
1565 programs which could be improved such as Keto or FMD etc.

1566      The dietary program must be continuously tested and developed at scale across institutions  
1567      where targeted precision nutrition programs can really benefit individuals: schools, hospitals,  
1568      prisons, elder care, and corporate environments. Only then will we see a systemic shift  
1569      towards nutritional plans which support brain health and metabolic wellness.

1570      To summarise:

## 1571    **1. Food Matrix & Precision Nutrition**

- 1572      • Understanding food matrix interactions is central to precision nutrition.  
1573      • Leveraging this science can help correct dysregulated biological systems targeted by the  
1574      BRAIN Diet, with implications for ADHD, cognitive health, metabolic health, and  
1575      neurodegenerative disease risk.  
1576      • Future research must expand laboratory studies into food matrix interactions and adopt FAIR  
1577      data principles to accelerate open collaboration.

## 1578    **2. Personalization & Diagnostics**

- 1579      • Diagnostic tools can guide personalization.  
1580        o Food sensitivity testing (IgG/IgA, elimination protocols) can uncover immune or  
1581        behavioral triggers.  
1582        o Genetic SNP testing (MTHFR, COMT, BDNF, CLOCK, PER3, FADS1/2) can reveal  
1583        individual predispositions that shape diet response..

## 1584    **3. Elimination Diets Reframed**

### 1585    **Conventional Elimination Diets**

Remove all common allergens

Evaluate only short-term behavior

Food seen as risk factor

Limited nutrient attention

One-size-fits-all exclusion

No long-term sustainability

### The BRAIN Diet Approach

Identify and remove individual triggers

Target biological systems (gut, neuroinflammation, methylation, dopamine balance)

Food used as precision intervention

Optimize for nutrient density, synergy, and repair

Personalized functional medicine approach

Designed for lifelong brain health and adaptability

1586 .

## 1587    **4. Accessibility & Practical Application**

- 1588      • Adherence is about sustainable patterns, not perfection.  
1589      • Algorithms guiding weekly menus will be openly published and AI-assisted.  
1590      • Leaning on plant proteins improves affordability and reduces health risks linked to excess red  
1591      meat.

1592 **5. Nutrient Sufficiency Across Diet Types**

- 1593 • Certain neuroprotective nutrients (e.g., creatine, taurine, carnitine) are abundant in animal  
1594 foods.  
1595 • Trials offering both omnivorous and plant-based versions will clarify whether observed  
1596 benefits stem from animal-derived nutrients or compensatory advantages of plant-based diets  
1597 (e.g., lower inflammation).

1598 **6. Functional Foods & Innovation**

- 1599 • Functional foods (e.g., sprouted grains, functional breads, probiotic dairy, UV-grown  
1600 mushrooms, functional ice creams) fit within a systems framework, not as isolated solutions.  
1601 • Emerging technologies (microencapsulation, precision fermentation, biofortification) offer  
1602 delivery advantages but must complement, not replace, diverse whole-food patterns.

1603 **7. Broader Health & Societal Impact**

- 1604 • Since the systems addressed overlap with cardiovascular and metabolic health, the BRAIN  
1605 Diet also supports healthy ageing and lifespan.  
1606 • Implementation at scale across schools, hospitals, prisons, elder care, and workplaces could  
1607 drive systemic change in mental and metabolic wellness.

1608 **8. Call for Open Collaboration**

- 1609 • Nutrition science must move beyond publication into **shared, open knowledge** that is  
1610 integrated into practice.  
1611 • The BRAIN Diet can serve as a vehicle for collaboration across microbiome research,  
1612 neuronutrition, metabolic health, and food science.  
1613 • Clinical trials and deeper research into the food matrix remain essential. Many of the  
1614 biological mechanisms discussed below, such as gut microbiome composition, gut-brain axis  
1615 dynamics, and neurotransmitter regulation, are still emerging fields. They require further  
1616 exploration through larger, more nuanced human studies to strengthen their clinical relevance,  
1617 but some positive human studies exist and much preclinical research indicates dietary  
1618 interventions could be highly beneficial (Ciancarelli 2024).

1619

1620 As Ferran Adrià noted in the 2014 foreword to Nathan Myhrvold's *Modernist Cuisine* series, "Now  
1621 is a good time to rethink how we teach cooking in schools... this lays a stepping stone to the future of  
1622 cooking." A decade later, as advances in microbiome research, neuronutrition, metabolic health,  
1623 genomics, and food science continue to accelerate, these fields must converge into a cohesive whole.  
1624 The need for open collaboration, integration, and socialisation has never been greater. The BRAIN  
1625 Diet offers one such vehicle.

## Supplementary Modules

1626

1627 **Breakdown of the BRAIN dietary framework. (figure 1).**

1628 **Before we eat (Lifestyle and Food choices):**

- 1629 1. Sustainability - – out of the scope of this paper but linked to plant based eating.
- 1630 2. Contamination - Where we source our food from can indicate levels of certain pollutants i.e.
- 1631 metals such as cadmium and lead are high in chocolate from central and south America (Godebo et
- 1632 al. 2024) though an USA analysis found vegetable and cereal products most affected by
- 1633 industrial and environmental sources of contamination (Hands et al. 2024).
- 1634 3. Histamine and Food Sensitivities (Histamine load and intolerance, using DAO co-factors like
- 1635 vitamin C & B6, ). Gluten, IgE, IgG responses to food.(NHS, n.d.)
- 1636 4. Lifestyle Factors (Sleep , exercise etc)

1637 **Food Choice by timing:**

- 1638 5. Circadian Influence (e.g. meal timing, sleep-wake cues)
- 1639 6. Additional Dietary Strategies – These can be implemented If blood results dictate or a period of
- 1640 dietary inadherence suggests a particular dietary focus is needed i.e. to counter a period: low in
- 1641 omega 3s, high inflammatory foods, or a lack of microbiome supporting nutrients.

1642 **Food Matrix Interactions:**

- 1643 7. Food Matrix Effects
- 1644 8. Precursors and cofactors (L-DOPA for dopamine)
- 1645 9. Food Synergies (e.g. Turmeric + black pepper; omega-3 fatty acids needs to be esterified to
- 1646 phospholipids to cross BBB, Non-heme Iron + vitamin C)
- 1647 10. Vitamin & Mineral Compatibility ( Vitamin D improves calcium absorption; vitamin C enhances
- 1648 iron uptake from plant sources. Consuming fat with fat -soluble vitamins (A, D, E, K);)
- 1649 11. Bioavailability isoquercetin (glycosylated quercetin) is more completely absorbed than quercetin
- 1650 in the aglycone form, vitamin C improves quercetin bioavailability. Bioavailability depends upon
- 1651 many factors from individual genetics to food matrix and drug interactions.

**Confidential**

1652 **Food Components**

- 1653 12. Carbohydrate Complexity (resistant, soluble, fermentation potential)
- 1654 13. Anti-Inflammatory Index (e.g. omega-3, curcumin Fodmap)
- 1655 14. Antioxidant Composition (e.g. glutathione, flavonoids, polyphenols)
- 1656 15. Fat Composition (e.g. omega-3 to omega-6 ratio, MCTs, olive oil, avocado oil)
- 1657 16. Protein Composition and quality (e.g. achieving complete amino acid profiles i.e. Pair legumes
- 1658 with grains (e.g., beans + rice) to cover lysine and methionine gaps., digestibility, )
- 1659

1660 **Biologic Targets**

- 1661 17. Insulin Response (e.g. glycemic load impact)
- 1662 18. Microbiome Impact (e.g. SCFA production, prebiotics)
- 1663 19. Hormonal Influence (e.g. insulin, cortisol, leptin sensitivity)
- 1664 20. Mitochondrial Support (e.g. CoQ10, etc))
- 1665 21. Neurotransmitter Support (e.g. tryptophan, choline)
- 1666 22. Methylation & Epigenetic Modulation (e.g. B12, folate, betaine)
- 1667 23. Endocannabinoid System Regulation (e.g. FAAH inhibition, omega-3)
- 1668 24. Reduce glycation end products (RAGE effects) by reducing glucose spikes.

1669

1670 **Detox Agents/Methods**

- 1671 25. Chelating (reducing metals via dietary intervention) (e.g. chelating agents: polyphenols,  
1672 chlorella, selenium, avoiding metals/ /pesticides/antibiotics/) .  
1673 26. Nutrient Preparation – reducing antinutrients, Polycyclic aromatic hydrocarbons etc.  
1674 27. Preservation Science – linked to increasing bioavailability.  
1675 28. Mindful Eating – Potential to improve digestion , reduce stress, increase oxytocin.

1676

1677 ***The dietary algorithm***

1678 The trained large language model (LLM), will be trained in the knowledge of those subjects  
1679 represented in Figure 1. The algorithm must be able to calculate individual variables and preferences  
1680 including: age, activity level, exercise habits, any known ADHD-related and other relevant genetic  
1681 polymorphisms (e.g., *MTHFR*, *MAOA*, *VAL66MET* etc). These personalized inputs will guide food  
1682 pairings and nutrient recommendations.

1683 Because the actual bioavailability of nutrients depends on numerous interacting factors, many of  
1684 which are still under investigation, the algorithm must draw from the best available data as presented  
1685 within current regulatory labelling systems. Optimization of nutrient distribution across meals will be  
1686 guided by a knapsack-style model to balance precision with feasibility, defaulting to representative  
1687 values based on nutrient type, preparation method, and commonly observed food pairings.

1688 The knapsack-style algorithm will be designed to evaluate and assemble food combinations that  
1689 collectively optimize a predefined set of key nutrients as outlined in this paper. Rather than  
1690 optimizing just individual meals in isolation, the algorithm **operates across meals throughout each**  
1691 **day and over multiple days**. All dietary targets will be met over the course of each weeks meal  
1692 plans, with nutrient timing strategies (e.g., BID dosing of short half-life nutrients) being factored in,  
1693 compensatory pairing of meals, and personalized adjustments based on metabolic, genetic, or  
1694 behavioral factors.

1695 The fundamental vitamin and mineral RDAs will be based upon dietary guidelines i.e. WHO, BANT  
1696 with any adaptations based upon evidence, meal proportions in terms of percentage of protein,  
1697 carbohydrates, fats etc will be based upon these recommendations with reasonable shifts to keep  
1698 meals balanced and to target the dietary principles outlined in this paper. For upcoming clinical  
1699 trials the algorithm will aid the dieticians and chefs with meal plans to leverage the research areas in  
1700 figure 1 including the key biological and nutritional information and interactions highlighted in this  
1701 paper which will, alongside other supporting evidence, be used to train the LLM.

1702 For individuals using the algorithm it will be possible to target any meals based upon personal or  
1703 nutritionist guided strategies to support the biological targets defined in the paper i.e. if inflammation  
1704 follows a period of eating pro-inflammatory foods then meals focusing on antioxidant rich foods and  
1705 endogenous antioxidant precursors can become a focus of each meal for a defined short period that  
1706 would not negatively affect other brain health goals.

1707

1708 ***Micronutrient Absorption***

1709 We note some are key considerations such as the vitamin and mineral synergies which need to be  
1710 factored into the diet to support brain health:

1711 **Vitamin C**, - significantly improves non-heme iron absorption by reducing ferric to ferrous iron,  
1712 with studies showing up to a fourfold increase when consumed together (Hallberg et al., 1989).

1713 **Vitamins A, D, E and K** - Dietary fat enhances the absorption of these fat-soluble vitamins  
1714 (Tangpricha et al., 2003),

1715 **Zinc and magnesium** – will compete and high-dose supplementation has been observed to  
1716 reduce absorption efficiency, warranting staggered intake when clinically necessary (Arnaud,  
1717 2008).

1718 **Iron** - is an essential cofactor for tyrosine hydroxylase, the rate-limiting enzyme in the conversion  
1719 of tyrosine to dopamine (Beard et al., 2003; Erikson et al., 2000). Pairing plant-based iron sources  
1720 with citrus, fat-soluble vitamins with avocado or olive oil, or spreading minerals across meals are  
1721 simple but impactful strategies that support maximising dietary nutrition.

1722 Proper preparation techniques — such as **soaking, fermenting, sprouting, or cooking** —  
1723 dramatically reduce the levels of problematic compounds while preserving or enhancing the  
1724 bioavailability of beneficial nutrients., making them less of a blanket concern and more a question of  
1725 dietary context. Similarly, tannins and saponins may inhibit nutrient uptake but also have anti-  
1726 inflammatory, antimicrobial, and anti-carcinogenic effects.

1727 From a brain health perspective, the primary concerns are antinutrients that significantly impair the  
1728 availability of iron, zinc, magnesium, and B vitamins—nutrients critical for neurotransmitter  
1729 synthesis, myelination, and mitochondrial function. For individuals with ADHD or cognitive  
1730 impairments, diets overly reliant on high-phytate or high-oxalate foods without preparation methods  
1731 like soaking, fermenting, or boiling could exacerbate mineral imbalances. However, when traditional  
1732 preparation techniques are used, the potential downsides of antinutrients are largely mitigated  
1733 allowing their possible protective and regulatory roles to be retained without compromising brain-  
1734 supportive nutrition.

1735 ***Cooking and Preparation methods to reduce oxidants and antinutrients***

1736 Alongside nutrient pairing, cooking methods and fat choices play a crucial role in the  
1737 nutritional quality of meals. While it is commonly held that steaming, baking, or light sautéing  
1738 helps maintain nutrient density and antioxidant content, sometimes larger benefits maybe  
1739 gained from boiling i.e. reducing oxalates and phytates in green vegetables such as spinach and  
1740 kale (Chai and Liebman 2005).

1741

1742 Because the BRAIN diet specifically targets leafy green vegetables i.e. kale and spinich that are  
1743 rich in iron, magnesium, and zinc this can introduce high dietary oxalate. Oxalate binds to these  
1744 minerals and forms insoluble compounds, which significantly reduces their bioavailability,

1745 (Chaiyarat and Thongboonkerd 2020) also found that oxalate (CaOx crystals and NaOx)  
1746 negatively affects mitochondrial function and changes redox status in monocytes while also  
1747 affecting mitochondrial function.

1748

1749 While concerns that oxalate causes stones is often inflated, as only about 10% of people will  
1750 ever develop these in their lives (with 80% of those being oxalate crystal related), and only  
1751 about 2% of people are oxalate sensitive, the diet should feature meals that reduce the  
1752 absorption of oxalate and support the good foundational gut bacteria which help process  
1753 oxalate (Daniel et al. 2021).

1754

1755 Highly processed seed oils, such as soybean, sunflower, and corn oil, are high in omega-6 fatty  
1756 acids, which are unstable at high temperatures and proinflammatory. When heated, these oils  
1757 undergo oxidation, producing harmful lipid peroxides and advanced glycation end products  
1758 (AGEs) (Uribarri et al. 2010). These compounds act as local initiators of inflammation, triggering  
1759 cellular signaling pathways that increase production of pro-inflammatory cytokines, such as  
1760 interleukin-6 (IL-6). Elevated IL-6 activates microglia, the brain's immune cells, leading to a  
1761 state of neuroinflammation. This process has been implicated in altering neurotransmitter  
1762 function, synaptic plasticity, and dopaminergic signaling ((Ramsden et al.  
1763 2013); (Schwingshakl and Hoffmann 2014)).

1764

1765 Replacing industrial seed oils with more stable options like olive oil, ghee, or avocado oil,  
1766 especially for low- to medium-heat cooking, may reduce inflammatory load while preserving  
1767 beneficial polyphenols. The strategy of simply adding parsley when cooking food has seen  
1768 significant reductions in harmful COPs (Cholesterol Oxidation Products) (de Oliveira et al.  
1769 2022).

### 1770 ***Soaking strategies to reduce phytates***

---

1771

### 1772 **Table X – Summary of Current and Topical Food Preparation & Interaction Strategies**

---

### 1773 **Relevant to Brain Health**

1774

1775

1776 Besides cooking techniques, preparation techniques can also maximise nutrients and reduce  
1777 negative food content and synergy effects. Soaking and sprouting grains is one such method to  
1778 increase the bioavailability of iron by reducing phytates, the germination of grains increases  
1779 antioxidant and nutritional value also. (Luo and Xie 2014). Just soaking beans at the right  
1780 temperature and pH level can activate endogenous phytases reducing the phytate content

1781 'Optimal conditions for the endogenous phytases of black beans, is 60C and pH 6.0, that resulted in  
1782 a 55% reduction in 1P6 after soaking and cooking. (GREINER and KONIETZNY 1999).

1783

Step	How	Why It Helps
<b>1. Rinse and soak beans</b>	Soak <b>dried beans</b> in <b>filtered warm water</b> (~50–60°C, or ~120–140°F) for <b>12–24 hours</b> . Keep warm in a thermos or low oven.	Activates <b>natural phytase</b> enzymes in the beans
<b>2. Add a mild acid (optional but helpful)</b>	Add a bit of <b>lemon juice or apple cider vinegar</b> (1–2 tsp per liter of water) to reach ~pH 5.5–6.	Optimizes pH for phytase enzyme activity
<b>3. Replace soaking water</b>	After soaking, <b>discard the water</b> , rinse beans well.	Removes dissolved phytates and anti-nutrients
<b>4. Cook thoroughly</b>	Boil the beans in fresh water until soft. <b>Do not use soaking water</b> for cooking.	Heat completes the breakdown of residual phytates
<b>5. Pair with vitamin C</b>	Eat your beans with <b>vitamin C-rich foods</b> (e.g., tomatoes, peppers, citrus)	Vitamin C <b>enhances non-heme iron absorption</b> even in the presence of phytates

1784

1785 Table 9 – Domestic procedures to reduce phylates to increase bioavailability of iron and zinc

1786

### *Bread and Food Matrix effects example*

1788 Bread making is an example of how food preparation strategies can have a positive effect on the  
1789 reduction of harmful cooking bi-products and the introduction of good bi-products. (Coda, Rizzello,  
1790 and Gobbetti 2010) demonstrate the fermentation of quinoa flour, and other functional flours,  
1791 introduces natural GABA; also with the addition of Glycine, a common industrial practice, harmful  
1792 acrylamide can also be reduced (Fink et al. 2006). Proteolytic events that occur during sourdough  
1793 fermentation affect the overall quality of bread, this process sees the sourdough fermentation  
1794 enhances bioavailability of amino acids through activation of endogenous cereal proteases under  
1795 acidic conditions (Gänzle, Loponen, and Gobbetti 2008), and in some cases, microbial proteases  
1796 from lactic acid bacteria. This enzymatic activity is also associated with increased digestibility and  
1797 reduced immunogenicity of gluten peptides. By considering the synergy of ingredients, the optimal  
1798 application of time and heat, and the details within the cooking i.e. closed cooking pot i.e. dutch  
1799 over opposed to open oven; the end product will reap several synergistic health benefits (Table 11  
1800 below).

1801

Component / Step	Purpose / Action	Effect on MRP / Acrylamide / Antioxidants/Health
<b>Whole Spelt Flour</b>	-High asparagine + fiber; substrate for Maillard; better MRPs than white flour	↑ Melanoidin precursors; ↑ antioxidant MRPs

Component / Step	Purpose / Action	Effect on MRP / Acrylamide / Antioxidants/Health
<b>Whole Wheat Flour</b>	-Gluten strength; more amino acids to fuel Maillard reaction	↑ Free amino acids; balanced reaction profile
<b>Pseudo Grains</b>	Quinoa, amaranth etc can introduce GABA and other important brain nutrients	↑ increase GABA and vitamins and minerals
<b>Glycine (0.3–0.4%)</b>	-Reduces acrylamide by competing with asparagine; encourages safer browning  -Introduces Lactic Acid Bacteria LAB which degrades asparagine; lowering acrylamide risk.	↓ Acrylamide formation; redirects Maillard toward safer end-products
<b>Sourdough Starter (100% hydration)</b>	-Increases SCFA precursors + microbial diversity, -Slower starch breakdown, supports glucose metabolism	↓ Asparagine via enzymatic degradation; gut microbiome support, ↓ Phytates broken down, especially in whole grains ↓ Lowers glycemic impact
<b>Honey or Malt Syrup (small amt)</b>	-Provides reducing sugars for Maillard; moderate dose helps antioxidant MRP formation	↑ Maillard activity in balance; enhances melanoidin production
<b>Sea Salt</b>	-Flavor + essential minerals; may slightly influence water activity	Neutral; supports flavor and mineral profile
<b>Filtered Water (72–76% hydration)</b>	-Supports Maillard without over-drying crust; helps suppress acrylamide	↑ Moisture retention = ↓ crust acrylamide; ↑ safe Maillard reaction
<b>Cold Fermentation (~12–18h)</b>	-Releases free amino acids; promotes natural proteolysis; lowers asparagine	↑ MRP diversity; ↓ acrylamide via extended fermentation
<b>Dutch Oven Baking (Enclosed)</b>	-Steam traps moisture; reduces crust temperature; slows acrylamide formation	↓ Acrylamide; ↑ antioxidant MRPs; gentle crust formation
<b>Bake Temp (230°C → 210°C)</b>	-Optimized heat curve for melanoidin formation; avoids excess acrylamide	↑ Browning compounds (melanoidins); ↓ harmful byproducts from excessive heat
<b>Final Crust (Golden Brown)</b>	-Promotes Maillard without carbonisation; visible indicator of antioxidant peak	Ideal MRP formation; acrylamide minimized via color monitoring

1802 **Table 11 - Ingredient & Method Table for making healthful Bread**

1803

1804

1805 **Proteins, muscle mass and Longevity**

1806 A meta study(Naghshi et al. 2020) found that intake of total protein was associated with a lower risk  
1807 of all cause mortality, and intake of plant protein was associated with a lower risk of all cause and  
1808 cardiovascular disease mortality, their study found that increasing the amount of plant proteins by 3%  
1809 of energy from plant proteins a day was associated with a 5% lower risk of death from all causes.  
1810 (Sun et al. 2019) found that by increasing 5% energy from animal protein with plant protein was  
1811 associated with a 13% lower risk of all-cause mortality, while substituting a four ounce  
1812 equivalent/day of total red meat with poultry, fish/shellfish, or nuts, was associated with a 8%, a  
1813 12%, and a 12% lower risk of all-cause mortality, respectively.

1814 While there are mixed results relating to the value of higher amounts of protein in health and  
1815 longevity, there are clearer positive signals to the correlation of muscle mass and longevity  
1816 (Srikanthan and Karlamangla 2014) and the associated health benefits, and longevity associated with  
1817 the reduction of sarcopenia(Coelho-Junior et al. 2022) and higher protein and exercise in combatting  
1818 anabolic resistance(Tezze, Sandri, and Tessari 2023) . Older adults may require higher protein intake  
1819 to prevent sarcopenia and functional decline (Houston et al. 2008) found that over 3 years the highest  
1820 quintile on approximately 1.1 g/kg/day of protein per day over the lowest quintile: approximately  
1821 0.7 g/kg/day experienced a 40% less loss of lean mass.

1822

1823 **Table 1b – Protein Quality Scores (DIAAS %) and Limiting Amino Acids**

Food Source	DIAAS % (Adults)	Limiting Amino Acid(s)	Notes on Brain Health Relevance
Whey protein isolate	118–122	None	High leucine, supports BDNF and neurotransmitter synthesis
Milk (skim)	118	None	Balanced EAA profile, supports myelination
Egg (whole)	113	None	Rich in choline for acetylcholine synthesis
Beef	108–110	None	High creatine, iron, zinc
Scallops	107–110	None	High taurine content
Salmon	105–108	None	Rich DHA & EPA for membrane fluidity
Tuna	104–106	None	High in selenium, omega-3
Mackerel	103–105	None	Omega-3, vitamin D source
Cod	101–104	None	Lean protein, taurine
Soy protein isolate	92–96	Methionine	Isoflavones, plant-based EAA source
Lentils	65–70	Methionine, cysteine	Fiber, folate, iron
Chickpeas	64–69	Methionine	Fiber, magnesium
Pea protein isolate	88–100	Methionine	Good arginine content, plant-based
Spirulina	75–83	Methionine, lysine	Contains some bioactive peptides
Quinoa	83–87	Lysine (marginal)	Complete plant protein, magnesium-rich

1824

1825

1826

**Table 1c – Plant Protein Quality (DIAAS %) and Brain-Health Pairing Strategies**

<b>Plant Protein Source</b>	<b>DIAAS % (Adults)</b>	<b>Limiting Amino Acid(s)</b>	<b>Brain-Health Notes</b>	<b>Best Pairing for Completeness</b>
Soy protein isolate	92–96	Methionine	Supports neurotransmitter synthesis; contains isoflavones with neuroprotective potential	Combine with grains (e.g., rice) to boost methionine
Pea protein isolate	88–100	Methionine	High arginine, supports nitric oxide production and cerebral blood flow	Pair with grains or seeds rich in methionine
Quinoa	83–87	Lysine (marginal)	Magnesium-rich, supports energy metabolism and GABA function	Combine with legumes to boost lysine
Spirulina	75–83	Methionine, lysine	Contains antioxidant phycocyanin; potential anti-inflammatory effects	Pair with grains and legumes for balance
Buckwheat	75–80	Lysine (marginal)	High rutin content for vascular health	Combine with lentils or chickpeas
Lentils	65–70	Methionine, cysteine	High folate for methylation; fiber for gut-brain axis	Pair with rice, quinoa, or nuts/seeds
Chickpeas	64–69	Methionine	Good source of magnesium and iron	Combine with grains like barley or oats
Kidney beans	60–65	Methionine	Polyphenol-rich; supports gut health	Pair with whole grains or seeds
Almonds	47–52	Lysine	Vitamin E for antioxidant protection	Pair with soy or legumes
Pumpkin seeds	40–45	Lysine	High zinc content for neurotransmitter modulation	Combine with legumes for lysine boost

<b>Nutrient / Compound</b>	<b>Neurochemical Pathway</b>	<b>Potential ADHD Symptom Support</b>
Tyrosine	Dopamine synthesis	Focus, drive, executive function
Tryptophan	Serotonin synthesis	Mood, impulse control
Omega-3 (EPA/DHA)	Dopamine transport, membrane fluidity	Attention, mood stability
B6, B9, B12	Methylation → serotonin, dopamine	Energy, cognition, emotional reg.

Choline

Acetylcholine production

Memory, learning, attention

1829 Table 3 – ADHD Symptom support via neurochemicals support

1830

## 1831 **Sustainability**

1832 Importantly, a well-formulated vegan BRAIN Diet may offer distinct advantages in terms of  
1833 environmental sustainability, especially when grounded in regenerative agriculture and a wide  
1834 diversity of minimally processed plant foods. However, it is a misconception that all vegan foods are  
1835 inherently low-impact; factors such as processing intensity, long-distance transport, and monoculture  
1836 cropping must also be weighed, though whole foods are the focus; sometimes protein isolates and  
1837 ....may be necessary to create full food matrix synergies within meals.

1838 Equally, the **omnivore version of the BRAIN Diet is intentionally designed to be plant-forward**,  
1839 emphasizing seasonal produce, legumes, whole grains, nuts, and fermented foods, while using small  
1840 amounts of high-impact animal products (e.g., organ meats, shellfish, eggs, or oily fish) for their  
1841 nutritional density. This approach not only minimizes ecological footprint per nutrient delivered, but  
1842 also aligns with principles of **nutritional efficiency and dietary restraint**, which are central to  
1843 sustainable food systems. In both cases—vegan or omnivore—closing the nutrient gap is not simply  
1844 about substitution, but about **elevation**: selecting high-function, bioactive-rich foods that can meet  
1845 complex neurobiological demands. When done strategically, **brain health and environmental  
1846 stewardship can coexist** without compromise.

Aspect	Vegan BRAIN Diet	Omnivore BRAIN Diet
Core Focus	100% plant-based; relies on high-function, nutrient-dense whole foods	Primarily plant-based with targeted use of nutrient-dense animal foods
Protein Sources	Legumes, fermented soy, lupins, Mankai, seeds, whole grains, functional yeasts	Same as vegan + small amounts of shellfish, organ meats, pasture-raised eggs
Animal Products	None	Ethically sourced, high-nutrient-density options (e.g., liver, fish roe, sardines)
Supplementation Needs	Likely includes B12, DHA (from algae), possibly iron, zinc, creatine, coQ10	Possibly lower; B12, DHA, choline, creatine often obtained from food. Probable benefits in omega 3 daily or minimum x3 upto 2mg per week.
Environmental Impact	Lower greenhouse gas emissions overall—but varies by crop source & processing	Moderately higher footprint but offset by <b>minimal</b> use of high-impact animal foods
Food Sourcing	Regenerative, seasonal, low-processed plant foods preferred	Regenerative farming for animal inputs; nose-to-tail (offal sources having the highest nutrient levels in animal products (Latouch, Stasiak, and Siczek 2024)) and low-waste ethos encouraged

Aspect	Vegan BRAIN Diet	Omnivore BRAIN Diet
<b>Sustainability Trade-offs</b>	Risk of relying on ultra-processed vegan substitutes or monoculture crops	Risk of higher footprint if animal foods are overused or poorly sourced
<b>Best Practice Goal</b>	Maximize nutrient density via functional plants + strategic supplementation	Optimize nutrient delivery with <b>minimal, strategic animal intake</b>

1847 Figure 10 – Sustainability Overview of Vegan and Omnivore BRAIN diets

1848

1849

1850 Agarwal, Puja, Sue E. Leurgans, Sonal Agrawal, et al. 2023. “Association of Mediterranean-DASH  
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