

# Forté Brain Protect™

**Science-based  
Nutritional Support for Improved Brain Resilience**

## PREPARE

## brain protect

## Nutritional support for improved brain resilience

**Acute and Chronic Brain Injury**

Traumatic brain injury (TBI) is a global public health epidemic. In the US alone, more than 3 million people sustain a TBI annually. It is one of the most disabling injuries as it may cause motor and sensory deficits and lead to severe cognitive, emotional, and psychosocial impairment, crippling vital areas of higher functioning. In many cases, a TBI results in death.

Acute or chronic injury to the brain, particularly if the injury is repetitive, can lead to a significant loss of neural tissue. This chronic loss of brain tissue leads to a permanent deficit.<sup>1</sup> To get a better sense of the problem, below are some sobering statistics.

- In 2013, about 2.8 million TBI-related emergency department (ED) visits, hospitalizations, and deaths occurred in the United States.<sup>2</sup>
  - TBI contributed to the deaths of nearly 50,000 people.
  - TBI was a diagnosis in more than 282,000 hospitalizations and 2.5 million ED visits. These consisted of TBI alone or TBI in combination with other injuries.
- In 2012, an estimated 329,290 children (age 19 or younger) were treated in U.S. hospitals for sports and recreation-related concussion or TBI.<sup>3</sup>
- From 2001 to 2012, the rate of hospital visits for sports and recreation-related diagnosis of concussion or TBI more than doubled among children (age 19 or younger).<sup>4</sup>

Fueled by the recognition of TBI as the “signature injury” in our wounded soldiers in Iraq and Afghanistan, and its often-devastating impact on athletes playing contact sports, interest in TBI and TBI research and education has increased. Significant time, energy, and money have been expended trying to find ways to mitigate brain injury, improve brain resilience to injury and possibly find ways to stimulate the regenerative potential of neural stem cells.<sup>5</sup> While there is significant progress being made to better understand TBIs, as you will see from the data, we aren’t doing very well when it comes to prevention.

***What does it take to get a concussion?***

The Centers for Disease Control and Prevention (CDC) defines a concussion as a “type of traumatic brain injury—or TBI—caused by a bump, blow, or jolt to the head or by a hit to the body that causes the head and brain to move rapidly back and forth. This sudden movement can cause the brain to bounce around or twist in the skull, creating chemical changes in the brain and sometimes stretching and damaging brain cells”.<sup>6</sup> There are 21 symptoms that have been identified that are caused by a concussion. Because no two concussions are exactly alike, and symptoms are not always definite, the injury’s severity, effects, and recovery are sometimes difficult to determine.

1- Hoff PR, Morrison JH. The aging brain: monomolecular senescence of cortical circuits. *Trends Neurosci* 2004; 27:607-613.

2- Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic Brain Injury–Related Emergency Department Visits, Hospitalizations, and Deaths – United States, 2007 and 2013. *MMWR Surveill Summ* 2017;66(No. SS-9):1–16. DOI: <http://dx.doi.org/10.15585/mmwr.ss6609a1>

3- Coronado VG, Haileyesus T, Cheng TA, Bell JM, Haarbauer-Krupa J, Lionbarger MR, Flores-Herrera J, McGuire LC, Gilchrist J. Trends in sports- and recreation-related traumatic brain injuries treated in US emergency departments: The National Electronic Injury Surveillance System–All Injury Program (NEISS–AIP) 2001–2012. *J Head Trauma Rehabil* 2015; 30 (3): 185–197.

4- *ibid*

5- Jessberger S. Neural repair in the adult brain. 2016 Feb 12,5. *Pii F1000 Faculty Rev* – 169.

6- Retrieved from [https://www.cdc.gov/headsup/basics/concussion\\_what.html](https://www.cdc.gov/headsup/basics/concussion_what.html)

It has been demonstrated that a single season of American high school football resulted in changes in magnetic resonance imaging indicative of axonal injury in the absence of a concussion diagnosis. In their recent position statement, the American Medical Society for Sports Medicine suggested that protective equipment does not reduce the incidence and/or severity of concussion in sport despite advancements, highlighting the need for different approaches to prevent brain damage.<sup>7</sup>

**Is brain injury always associated with a concussion?**

Brain injury often occurs in the absence of actual concussion. It is often referred to as Mild Traumatic Brain Injury (MTBI). Concussion and MTBI are often used interchangeably. These mechanical forces are known to result in acceleration and deceleration forces on neurons, supporting cells and their projecting fibers, as well as intra-cellular injury, which leads to diffuse axonal injury. The presence of axonal injuries can be monitored by measuring specific “bio-markers” in the blood stream. This methodology has proven to be an important mechanism to measure the extent of brain injury and to monitor response to various treatment regimens.

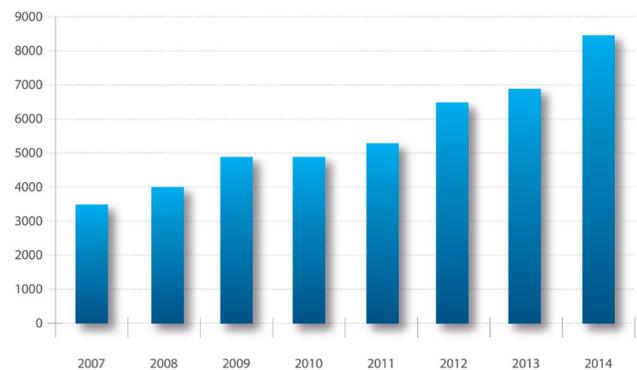
**Concussion symptoms and findings**

Most concussion symptoms are reported to resolve within 7-10 days. Studies have shown that 33% of concussion victims suffer from persistent symptoms for more than 6 months while 15% report symptoms for up to 12 months following injury. Concussion can lead to damage in the white matter of the brain that resembles abnormalities found in people in the early stages of Alzheimer’s disease. In one study, the University of Pittsburgh School of Medicine said their findings should prompt a re-evaluation of the long-term effects of concussion, which affects more than 1.7 million people in the United States annually. About 15% of concussion patients suffer persistent neurological symptoms.<sup>8</sup>

**Concussion and TBI Rates on the Rise**

New research is suggesting the modern brain is less resilient to traumatic impact than in previous decades. As partial evidence, incidences of concussions are dramatically increasing – not just among athletes, but in the general population as well.<sup>9, 10, 11</sup>

The Rise in Concussion Rates



The Rise of Concussions in the Adolescent Population. Investigation performed at the University of California. <http://journals.sagepub.com/doi/pdf/10.1177/2325967116662458>

7- Harmon KG, Drezner JA, Gammons M Endorsed by the National Trainers’ Athletic Association and the American College of Sports Medicine, et al American Medical Society for Sports Medicine position statement: concussion in sport Br J Sports Med 2013;47:15-26.  
 8- Henry LC, Tremblay S, DeBeaumont L. (2016). Long-Term Effects of Sports Concussions: Bridging the Neurocognitive Repercussions of the Injury with the Newest Neuroimaging Data. Neuroscientist. 2016 May 17 pii: 1073858416651034  
 9- Summary of the WHO Collaborating Centre for Neurotrauma Task Force on Mild Traumatic Brain Injury. Holm L, Cassidy JD, Carroll LJ, Borg J, Neurotrauma Task Force on Mild Traumatic Brain Injury of the WHO Collaborating Centre. J Rehabil Med. 2005 May; 37(3):137-41.  
 10- The epidemiology and impact of traumatic brain injury: a brief overview. Langlois JA, Rutland-Brown W, Wald MM J Head Trauma Rehabil. 2006 Sep-Oct; 21(5):375-8.  
 11- Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. McCrory P, Meeuwisse WH, Aubry M, Cantu B, Dvorák J, Echemendia RJ, Engebretsen L, Johnston K, Kutcher JS, Raftery M, Sills A, Benson BW, Davis GA, Ellenbogen RG, Guskiewicz K, Herring SA, Iverson GL, Jordan BD, Kissick J, McCrea M, McIntosh AS, Maddocks D, Makdissi M, Purcell L, Putukian M, Schneider K, Tator CH, Turner M Br J Sports Med. 2013 Apr; 47(5):250-8.

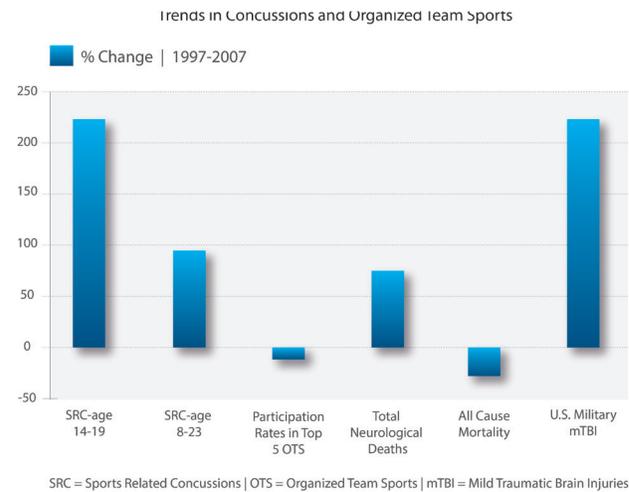
Across the population, there is a significant rise in concussions, TBIs, and other related neurological disorders and related deaths. The Centers for Disease Control and Prevention (CDC) estimates that as many as 3.8 million sports and recreation brain injuries occur annually in the United States alone. Additionally, neurological deaths are increasing disproportionately to total mortality rates.

Looking at just sports-related concussions provides some added insight. For example, sports-related concussions in the United States youth and young adult population are on the rise; however, participation in sports among youth and young adults is on the decline.<sup>12</sup>

Looking at NCAA athletes, between 2009 and 2014, NCAA athletes reported 10,500 concussions. Of those brain injuries, only 32% of them occurred in football.<sup>13</sup>

In addition to SRC increases, another group that has seen a significant disproportionate increase in concussions, TBIs, and neurological deaths is the military. Between 2000 and 2010, total TBIs increased 233%.<sup>14</sup> Between 2000 and 2013, American Armed Service members reported 320,000 brain injuries, 80% of those injuries occurred outside of combat.

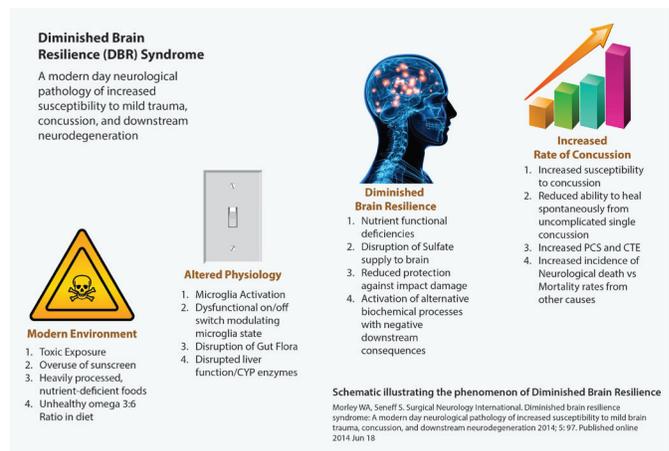
This begs the question, why? With so much more investment in research, protective equipment, education, and awareness – why is the risk increasing and not declining?



Source: data retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4093745/>  
 Data gathered from Bakhos LL, Lockhart GR, Myers R, Linakis JG. Emergency department visits for concussion in young child athletes. *Pediatrics*. 2010;126:e550-6 and Pritchard C, Meyers A, Bablitz D. Changing patterns of neurological mortality in the 10 major developed countries 1979-2010. *Public Health*. 2013. and The Defense and Veterans Brain Injury Center website.

## Diminished Brain Resilience Syndrome

Researchers Wendy A. Morley and Stephanie Seneff wondered why concussions, TBIs, and other neurological disorders and deaths were on the rise. In 2014, Morley and Seneff released their landmark research in the medical journal "Surgical Neurology International" following a double-blind peer review process. The core findings illustrate not only that the modern brain has a diminished resilience capacity, but key reasons why have developed and identified a possible reason to explain the increase in concussions and other traumatic brain injuries. They refer to the problem as Diminished Brain Resilience Syndrome (DBR).<sup>15</sup> Based on significant secondary research, the data suggest the modern brain is more vulnerable than brains of only a decade ago.



12- Bakhos LL, Lockhart GR, Myers R, Linakis JG. Emergency department visits for concussion in young child athletes. *Pediatrics*. 2010 Sep; 126(3): e550-6.

13- Retrieved from <http://www.ncaa.org/about/resources/media-center/feature/concussion-and-college-sports>

14- Retrieved from Defense and Veterans Brain Injury Center. <http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi>

15- Morley WA, Seneff S. *Surgical Neurology International*. Diminished brain resilience syndrome: A modern day neurological pathology of increased susceptibility to mild brain trauma, concussion, and downstream neurodegeneration 2014; 5:97. Published online 2014 Jun 18. doi: 10.4103/2152-7806.134731 PMID: PMC4093745

Following are key problems they have identified as possible reasons contributing to a lack of brain resilience.

1. The modern American diet has moved away from omega-3 fatty acids and toward more omega-6 fatty acids.
2. Increased exposure to both environmental toxins as well as toxins in our current food source due to fertilizers, weed killers, pesticides, herbicides, etc.
3. Diminished nutrients in our current food supply for the same reasons.

These researchers suggest our environment, lifestyle, and food sources may inhibit our body's inability to properly utilize key nutrients. Additionally, there has been a significant shift in the omega 3 to omega 6 fatty acid ratios that we ingest. The result? We are living with a depletion of neurocritical nutrients needed to achieve comparable brain resilience compared to prior decades.

Diminished Brain Resilience Syndrome results in:

- "Increased susceptibility to brain injury, by the priming of the microglia, a key step in immunoexcitotoxicity, which is strongly linked to mTBI, chronic traumatic encephalopathy (CTE), and other neurological disorders
- Reduced ability to appropriately modulate physiological response to brain injury, as a function of deficiencies in key micronutrients, such as magnesium, sulfur, and zinc, which are substrates or catalysts in the biochemical responses to brain injury
- Disruption and dysfunction of the normal 'on/off' regulation switching of biochemical processes engaged with brain injury
- Deficiency of neuro-essential fatty acids (neuro-EFAs), specifically docosahexaenoic acid (DHA), and of monoamine neurotransmitters, which leads to impaired antioxidant capacity and sulfate supply to the brain and associated pathologies
- Hyper-reactive excitatory response due to persistently primed microglia
- A chronic state of persistent secondary neurodegeneration, with an impaired ability to recycle cellular debris."<sup>16</sup>

## Neuroprotection - Improving Brain Resilience

The link between nutrition and cognitive performance stems from the knowledge that the central nervous system (CNS) relies on a constant supply of glucose and nearly all the essential nutrients for effective functioning.<sup>17</sup>

Nutrition plays a critically essential role in both short- and long-term brain health. Recent and significant research has highlighted the potential impact of nutritional factors and individual micronutrients on the brain, cognitive performance, and even the development of Alzheimer's disease, the most common form of dementia.<sup>18,19</sup> In fact, measures of brain electrophysiology

16- Morley WA, Seneff S. Surgical Neurology International. Diminished brain resilience syndrome: A modern day neurological pathology of increased susceptibility to mild brain trauma, concussion, and downstream neurodegeneration 2014; 5: 97. Published online 2014 Jun 18. doi: 10.4103/2152-7806.134731 PMID: PMC4093745

17- Selhub J, et al. B vitamins, homocysteine and neurocognitive function in the elderly. Am J Clin Nutr 2000;71(Suppl):614S-620S.

18- Nourhashemi F, Gillette-Guyonnet S, Andrieu S, Ghisolfi A, Ousset PJ, Grandjean H, Grand A, Pous J, Vellas B, Albaredo JL. Alzheimer disease: protective factors. Am J Clin Nutr. 2000 Feb;71(2):643S-649S.

19- Tucker, Don & A. Williamson, Peter. (1984). Tucker, D. M. & Williamson, P. A. Asymmetric neural control systems in human self-regulation. Psychol. Rev. 91, 185-215. Psychological review. 91. 185-215. 10.1037/0033-295X.91.2.185.

and behavior have been shown to be sensitive to even short periods of nutritional inadequacy.<sup>20, 21, 22</sup> Unfortunately, while most people are not underfed, when it comes to nutrition for the brain, many are mal-nourished.

### *Can nutrition have a neuroprotective affect against head trauma?*

There are significant bodies of research suggesting the key nutrients provides significant neuroprotective benefits. Current nutritional science demonstrates we can and should take the following steps.

1. Better prepare brain tissue to withstand injury and respond to injury by providing the nutritional elements known to improve brain resilience. Today's average lifestyle with a diet high in processed foods, frequent antibiotic use, and exposure to environmental toxins (herbicides/pesticides etc.) contributes to increased brain sensitivity to injury. Most patients have microglia (specialized brain cells) that are in a constantly primed state. This primed state leads to hyperactive microglia after even small traumatic incidences. Our ancestor's diet likely included much more fish, seafood, and greens, leading to a healthy 4:1 omega 6:3 ratio. The typical American diet, unfortunately, has an omega 6:3 fatty acid ratio of closer to 22:1 due to the large amount of omega-6 polyunsaturated fats from the vegetable oils used in packaged and processed foods. Given this ratio, it is believed that the risk to athletes aged 14-19 is significant. The relatively low omega-3 intake further reduces the amount of brain supporting EPA and DHA available in the diet increasing brain vulnerability.
2. Pre-load brain tissue with the metabolic components it needs to recover from brain injury.
3. Augment recovery after injury by aggressively supporting the known nutritional needs of injured brain tissue.

Following are specific elements that science has indicated will help with the above steps.

## **DHA – A Critical Neuroprotective Factor**

### *Why is DHA so important?*

DHA (the most prevalent omega-3 in the brain) and other free fatty acids play an important role in neural homeostasis. Anti-inflammatory benefits of omega-3 fatty acids (DHA) have been well documented. There is also evidence that omega-6 fatty acids lead to more inflammatory prostaglandin synthesis. omega-3 fatty acids are known to be critical for optimal brain health, function and resilience. Improving your omega-6/omega-3 ratio improves the availability of brain supporting DHA and reduces brain vulnerability before brain injury or concussion occurs.<sup>23</sup>

## **DHA and Football Induced Head Trauma: A Landmark Study**

There have been numerous rodent studies that indicate supplementation with DHA, either before or after brain injuries, suggest faster healing times by generating improved functional outcomes.<sup>24, 25, 26</sup>

20- Bronzino JD, et al. Power spectral analysis of the EEG following protein malnutrition. Brain Res Bull 1980; 5:51-60

21- Chafetz M.D. Nutrition and neurotransmitter; The Nutrient Basis of Behavior. Englewood Cliffs, NJ; Prentice –Hall, 1990.

22- Selhub J. et al. B vitamins, homocysteine and neurocognitive function in the elderly. Am J Clin Nutr 2000;71(Suppl)614S – 620S.

23- Mills JD, Hadley K, Bailes JE. Dietary supplementation with the omega-3 fatty acid docosahexaenoic acid in traumatic brain injury. Neurosurgery. 2011. 68: 474-81

24- Mills JD, Hadley K, Bailes JE. Dietary supplementation with the omega-3 fatty acid docosahexaenoic acid in traumatic brain injury. Neurosurgery. 2011;68(2):474-81.

25- Wu A, Ying Z, Gomez-Pinilla F. Dietary strategy to repair plasma membrane after brain trauma: implications for plasticity and cognition. Neurorehabil Neural Repair. 2014;28(1):75-84.

26- Barrett EC, McBurney MI, Ciappio ED. Omega-3 fatty acid supplementation as a potential therapeutic aid for the recovery from

In June of 2016, The American College of Sports Medicine published the study in *Medicine & Science in Sports & Exercise*.<sup>27</sup> This study was the first large-scale study examining the potential use of DHA in American football athletes to determine if there is a neuroprotective effect of DHA supplementation. The study was randomized, double-blind, and placebo-controlled using 81 NCAA division 1 football players. The study was conducted to look at both the effect of DHA as well as the dosage of DHA.

Because the force accompanying even a mild traumatic brain injury (mTBI) results in an elevation of serum neurofilament light (NFL), the researchers decided to use NFL levels as a biomarker of brain injury due to head impact.<sup>28</sup> With the NFL biomarker, researchers could determine if DHA supplementation would influence the American football players similar to what prior studies had determined in laboratory rodents.

Over the course of a season (189 days), one group of athletes was given a placebo while another group was given DHA. Of the group receiving DHA, both groups were further subdivided and given 2 grams, 4 grams, or 6 grams daily of either the placebo or DHA. The DHA used in the study was derived from algae as opposed to fish.

At the end of the study, the results were rather remarkable. Those athletes who received DHA over the placebo had attenuated NFL. During conference play, the most active part of the season increases in serum NFL was observed among the starting athletes. However, those taking the algae-based DHA had a likely 87.1% reduction of NFL compared to the athletes taking the placebo. As the season progressed, there was additional improvement resulting in up to 98.9% lowering effect.

Of the groups receiving either 2, 4, or 6 grams, those athletes receiving 2 grams per day had the greatest overall value regardless of physical size. Not only did the 2-gram dose produce the most marked reductions in serum NFL compared to the placebo, it also contributed to the largest decrease in arachidonic acid, another health benefit.

### *Evidence suggests chronically low DHA/EPA levels*

In a national study, researchers looked at long-chain omega-3 polyunsaturated fatty acid (LCn-3 PUFA) across all age groups in the United States. Plasma fatty acids were measured among 1386 subject years from the National Health and Nutrition Examination Survey, 2003–2004. Nearly all participants (95.7%) had LCn-3 below concentrations associated with cardiovascular protection.<sup>29</sup>

There have been several studies looking specifically at DHA/EPA levels in athletes and others. Using a simple blood test, researchers obtain an Omega-3 (DHA/EPA) Index showing specific levels of DHA/EPA. The Omega-3 Index uses reference ranges between 2.9% and 12.9%. There have been many tests conducted looking at DHA/EPA levels. In this paper, we will reference a sampling of some of the studies conducted that suggest an alarming problem.

In one clinical trial published in *The Journal of the American Heart Association* in 2013, the researchers conducted a randomized, placebo-controlled, double-blind, parallel-group study in 115 healthy men and women.<sup>30</sup> At the outset of the trial, the participants DHA/EPA levels

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mild traumatic brain injury/concussion. *Adv Nutr.* 2014;5(3):268–77.

27- Oliver JM, Jones MT, Kirk KM, Gable DA, Repshas JT, Johnson TA, Andréasson U, Norgren N, Blennow K, Zetterberg H. Effect of docosahexaenoic acid on a biomarker of head trauma in American football. *Med Sci Sports Exerc.* 2016 ;48(6) :974–82.

28- Davenport EM, Whitlow CT, Urban JE, et al. Abnormal white matter integrity related to head impact exposure in a season of high school varsity football. *J Neurotrauma.* 2014; 31(19): 1617–24.

29- Murphy RA, Yu EA, Ciappio ED, Mehta S, McBurney MI. Suboptimal Plasma Long Chain n-3 Concentrations are Common among Adults in the United States, NHANES 2003–2004. *Nutrients.* 2015; 7(12):10282–10289.

30- Flock, M. R., Skulas-Ray, A. C., Harris, W. S., Etherton, T. D., Fleming, J. A., & Kris-Etherton, P. M. (2013). Determinants of Erythrocyte

were measured. All 115 participants were below the 8% level, and most were 4% or below.

In another study, twenty-four elite summer sport athletes of both sexes training at the Olympic Training Center in Spain were tested for DHA/EPA levels. All but one athlete's blood DHA/EPA levels was below the low ideal of 8%.<sup>31</sup>

Another study in the participants were 106 German national elite winter endurance athletes using the Omega-3 Index to determine DHA/EPA levels. Only one athlete had a value within the target range – all other athletes were below 8%.<sup>32</sup>

As previously illustrated, DHA levels appear to be chronically low across all age segments throughout the United States. In the DHA and Football Induced Head Trauma study referenced above, the ideal amount of DHA added to the diets of those football players was 2000mg per day. In this study, the participants took algae-derived DHA for more than 6 months in achieving the neuroprotective results experienced.

In other studies, researchers looked at actual DHA/EPA blood levels using the Omega-3 Index referenced above. In these studies, they were able to look at a baseline EPA/DHA level and measure levels over time as participants took oral DHA supplements. The studies suggest it takes 2000mg of DHA/EPA per day for 4 months to bring DHA/EPA blood levels at a safe 8% or higher on the Omega-3 Index and to continue with 2000mg per day to maintain those levels.<sup>33, 34, 35, 36</sup>

## Other Neuroprotective Micronutrients

### Vitamin A

Plays an important role in cell-to-cell signaling in the brain<sup>37</sup> and provides neuroprotective functions of the neurons. The bioactive component of Vitamin A is retinoid acid which is a critical signaling molecule in the brain. Among other functions, these retinoid signaling pathways modulate neurogenesis, synaptic plasticity both crucial for a healthy brain that may be subject to impact. Additionally, retinoids provide protection for neuronal survival.<sup>38</sup>

Other critical brain functions supported by Vitamin A include support for the hippocampus and hypothalamus in memory and circadian rhythms functions.<sup>39</sup>

Vitamin A is also essential for activating Retinoid X Receptors (RXR) which are needed to activate

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- Omega3 Fatty Acid Content in Response to Fish Oil Supplementation: A Dose-Response Randomized Controlled Trial. *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease*, 2(6), e000513. <http://doi.org/10.1161/JAHA.113.000513>
- 31- Drobnic, F, Rueda, F, Pons, V, Banquells, M, Cordobilla, B, & Domingo, JC. "Erythrocyte Omega-3 Fatty Acid Content in Elite Athletes in Response to Omega-3 Supplementation: A Dose-Response Pilot Study," *Journal of Lipids*, vol. 2017, Article ID 1472719, 7 pages, 2017. doi:10.1155/2017/1472719
- 32- Von Schacky, C., Kemper, M., Hasibauer, R., Martin, H. "Low omega-3 index in 106 german elite winter endurance athletes: A pilot study," *International Journal of Sport Nutrition and Exercise Metabolism*, vol. 24, no. 5, pp. 559-564, 2014.
- 33- Drobnic F, Rueda F, Pons V, Banquells M, Cordobilla B, Domingo JC. Erythrocyte Omega-3 Fatty Acid Content in Elite Athletes in Response to Omega-3 Supplementation: A Dose-Response Pilot Study. *Journal of Lipids*. June 1, 2017.
- 34 - Oliver JM, Jones MT, Kirk KM, Gable DA, Repshas JT, Johnson TA, Andréasson U, Norgren N, Blennow K, Zetterberg H. Effect of docosahexaenoic acid on a biomarker of head trauma in American football. *Med Sci Sports Exerc*. 2016 ;48(6) :974-82.
- 35 - Watson H, Mitra S, Croden FC, Taylor M, Wood HM, Perry SI, Spencer JA, Quirke P, Toogood GJ, Lawton CL, Dye L, Dye L, Loadman PM, Hull MA. A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota. *Gut*. published online September 26, 2017
- 36 - Knöchel C, Voss M, Grter F, Alves GS, Silke M, Sepanski B, Stäblein M, Wenzler S, Prvulovic D, Carvalho AF, Oertel-Knöchela V. Omega 3 Fatty Acids: Novel Neurotherapeutic Targets for Cognitive Dysfunction in Mood Disorders and Schizophrenia? *Current Neuropharmacol*. 2015 Sep; 13(5): 663-680.
- 37- Lane MA, Bailey SJ. Role of retinoid signaling in the adult brain. *Progress in Neurobiology* 2005; 75:275-293.
- 38- Olson CR, Mello CV. Significance of vitamin A to brain function, behavior and learning. *Molecular Nutrition and Food Research*. 2010 Apr;54(4):489-95. doi: 10.1002/mnfr.200900246.
- 39- McCaffery P, Zhang J, Crandall JE.

the vitamin D receptors. In other words, vitamin A deficiency results in a vitamin D deficiency. Vitamin D (see below) is a critical vitamin to support neuroprotection.

### Vitamin C

When a concussion or TBI occurs it, the initial damage occurs due to the impact. Unfortunately, this initial damage elicits a stress response in the body releasing a flood of free radicals that further damage (oxidative damage) brain vital tissue.<sup>40,41</sup>

Vitamin C is a neuroprotective powerful antioxidant molecule in the brain combating free radicals. Pre-loading the body with vitamin C can potentially provide needed support in the event of a concussion or TBI to help mitigate post-injury risk of additional damage. As a zinc synergist, it supports additional antioxidant resources of the brain, synaptic activity, and detoxification.<sup>42</sup>

Additionally, vitamin C is critical in neuronal maturation and differentiation, myelin formation, synthesis of catecholamine, modulation of neurotransmission and antioxidant protection.<sup>43</sup>

The highest concentrations of Vitamin C in the body are found in the brain. Some evidence suggests that Vitamin C may change the course of neurological diseases and display potential therapeutic roles.

Vitamin C is essential in the production of neurotransmitters<sup>44</sup> which impact every aspect of life.

### Vitamin D

Vitamin D, a fat-soluble vitamin and as a neuroactive steroid is critical for brain function and neuroprotection. Research suggests vitamin D is neuroprotective through antioxidative mechanisms, neuronal calcium regulation and calcium-mediated neuronal excitotoxicity, immunomodulation, enhanced nerve conduction and detoxification mechanisms.<sup>45,46</sup>

In addition to the neuroprotective qualities of vitamin D, there are numerous other brain benefits. For example, though vitamin D deficiency has been linked to poor brain development,<sup>47</sup> sufficient vitamin D improves cognition,<sup>49</sup> reduces depression symptoms<sup>50</sup> among numerous other benefits.

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40- O'Connell KM1, Littleton-Kearney MT. The role of free radicals in traumatic brain injury. *Biological Research for Nursing*. 2013 Jul;15(3):253-63. doi: 10.1177/1099800411431823. Epub 2012 Feb 16.

41- Hall ED, Braughler JM. Free radicals in CNS injury. *Research Publications – Association for Research in Nervous and Mental Disease*. 1993; 71:81-105.

42- Gromova OA, Torshin IY, Pronin AV, Kilchevsky MA. Synergistic application of zinc and vitamin C to support memory, attention and the reduction of the risk of the neurological diseases. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2017;117(7):112-119. doi: 10.17116/jnevro201711771112-119.

43- Ibid

44- Harrison FE, May JM. Vitamin C Function in the Brain: Vital Role of the Ascorbate Transporter (SVCT2). *Free radical biology & medicine*. 2009;46(6):719-730. doi: 10.1016/j.freeradbiomed.2008.12.018.

45- Buell JS, Dawson-Hughes, B. Vitamin D and neurocognitive dysfunction: Preventing “Decline? *Molecular Aspects of Medicine*. Volume 29, Issue 6, December 2008, Pages 415-422

46- Mpandzou G, Ait Ben Haddou E, Regragui W, Benomar A, Yahyaoui M. *Revue Neurologique*. 2016 Feb;172(2):109-22. doi: 10.1016/j.neuro.2015.11.005. Epub 2016 Feb 8.

47- Groves NJ1, McGrath JJ, Burne TH. Vitamin D as a neurosteroid affecting the developing and adult brain. *Annual review of Nutrition*. 2014; 34:117-41. doi: 10.1146/annurev-nutr-071813-105557.

48- Harms LR, Burne TH, Eyles DW, McGrath JJ. Vitamin D and the brain. *Best Practices and Research. Clinical Endocrinology and Metabolism*. 2011 Aug;25(4):657-69. doi: 10.1016/j.beem.2011.05.009.

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50- Shaffer JA, Edmondson D, Wasson LT, et al. Vitamin D Supplementation for Depressive Symptoms: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Psychosomatic medicine*. 2014;76(3):190-196.

## Vitamin E

Brain injury is followed by oxidative damage and a proliferation of free radicals. The brain is highly susceptible to damage associated with oxidative stress caused by free radicals, which leads to neurodegeneration.<sup>51</sup> Vitamin E includes a group of eight structurally related, lipid-soluble, chain-breaking antioxidants—four tocopherols and four tocotrienols—that act as free radical scavengers making Vitamin E very neuroprotective. Alpha-tocopherol is the most abundant and bioavailable antioxidant form of vitamin E in human tissues.<sup>52</sup> Preloading your body with vitamin E can help mitigate damage caused by mTBI.

Research has repeatedly associated high plasma vitamin E levels with better cognitive performance.<sup>20</sup> In one study of approximately 15,000 women aged 70-79 years, those who took a combination of vitamin E and C supplements for 20 years had better cognitive performance than those who did not. And, those women who had been taking vitamin E and C supplements for the longest were found to be 1.5 years younger by cognitive age.<sup>53</sup>

The biological relevance and neuroprotective properties of vitamin E may extend beyond its antioxidant activity. More recently, vitamin E has been shown to play a critical role in signaling, membrane fluidity, and gene regulation.<sup>20</sup> Animal studies have shown that low alpha-tocopherol levels in the brain induce downregulation of genes involved in myelination, neuronal vesicle transport, and glial functions.<sup>54, 55</sup>

## Vitamin K2

Among the ways vitamin K2 contributes to brain and nervous system health includes its involvement in the activation of specific proteins that empower them to perform essential functions, anti-inflammatory properties, and sphingolipid metabolism, a class of lipids widely present in brain cell membranes.<sup>56, 57</sup>

There are about a dozen vitamin K dependent proteins (VKDP). Without vitamin K2, these proteins are unusable by the human body. Two of these proteins are Gas6 and protein S, both of which are closely associated with the brain and nervous system and demonstrate neuroprotective actions.<sup>58, 59</sup>

In recent years, studies suggest poor sphingolipid metabolism to cognitive decline and neurodegenerative diseases.<sup>60</sup>

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### Vitamin B1 (Thiamine)

Thiamine plays a key role in the maintenance of brain function,<sup>61</sup> and has been proven to not only have a positive effect on neurodegenerative diseases but is neuroprotective as well.<sup>62</sup> In fact, thiamine is required for neurons to generate energy. Conversely, not enough thiamine results in risk to all organ systems especially particularly the cells of the nervous system (e.g., neurons and glial cells, which are supporting cells in the nervous system).<sup>63</sup>

Thiamine deficiency can lead to oxidative stress, glutamate-mediated excitotoxicity, and inflammation.<sup>64</sup> Athletes who are under tremendous physical stress and exertion are at increased risk for thiamine deficiency which can lead to serious neurodegenerative diseases and a loss of protection for the entire CNS. In a mTBI inflammation, oxidative stress and excitotoxicity responses are triggered in the brain. Studies suggest a thiamine deficiency can lead to acceleration of neurodegeneration.

There have also been many studies that suggest thiamine supplementation post-concussion will minimize neurodegeneration and trauma because thiamine combats oxidative stress, excitotoxicity, and inflammation.<sup>65</sup> This suggests pre-loading with thiamine will reduce the risk of additional damage to the brain in the event of mTBI.

### Vitamin B6

Vitamin B6, along with the other B vitamins, are critical in converting food to energy, and essential in proper brain and nervous system function along with mental and emotional health. Among the many brain health benefits of Vitamin B6 includes its role in neurotransmitter production.<sup>66,67</sup> Neurotransmitters are essential chemicals that transmit signals from one cell to another and hormone production.<sup>68</sup>

B6 is essential for optimal brain and nervous system health. B6 deficiency has been linked to numerous mental health disorders including depression,<sup>69</sup> anxiety,<sup>70</sup> sleep disorders and cognition.<sup>71</sup>

### Folic Acid

Folic Acid is a form of folate which is also known as vitamin B9. As one of the B vitamins, it is essential in converting food to energy and widely known as critical to the brain development of a fetus.

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In adults, folic acid improves brain function, is essential to the rest of the nervous system, and support mental and emotional health. Deficiencies have been linked to problems with cognition,<sup>72,73</sup> depression,<sup>74</sup> and neurodegeneration.<sup>75</sup>

### Vitamin B12

Vitamin B12 is critical for maintaining nerve cells and works in conjunction with folic acid (see above) to support mental and emotional health. B12 is essential for memory, focus, and concentration and works with other elements, including folic acid to combat depression.<sup>76</sup> Because B12 is a cofactor in the synthesis of neurotransmitters such as serotonin and dopamine deficiencies affects mood, emotions, and sleep which can lead to psychiatric disorders.<sup>77,78</sup>

### Boron

Boron is a vitally essential trace element and provides an important role, directly and indirectly, in both the function and protection of the brain.<sup>79</sup> As part of the neuroimmune response following mTBI, a cascade of pro-inflammatory cytokines is released. There are numerous studies showing boron directly reduces inflammation,<sup>80,81</sup> thereby providing additional neuroprotective support.

In addition to direct anti-inflammatory support, boron is also a vitamin D agonist and boosts the body's use of vitamin D.<sup>82</sup> As established above, vitamin D is a powerful antioxidant as well as other beneficial neuroprotective qualities. Similarly, boron also boosts the use of magnesium, which also benefits the brain (see below).<sup>83</sup>

Studies of healthy individuals have shown that even relatively short periods of restricted dietary boron intake can have a negative impact on brain function and various cognitive and psychomotor tasks.<sup>84,85</sup> Restricted dietary boron intake has also associated with significantly poorer performance on tasks emphasizing manual dexterity, hand-eye coordination, attention, perception, as well as short and long-term memory, and long-term memory.<sup>86</sup>

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### Calcium

Most people are aware of the benefits of calcium for bones and teeth. Calcium is also important for a healthy brain and central nervous system (CNS). Calcium plays a role in supporting the electrical signals within the brain and nervous system. These signals are critical for the CNS to function properly.

Studies suggest calcium signaling impairment follows a TBI.<sup>87, 88</sup> Studies also suggest that preloading with calcium may have a beneficial neuro protective effect upon the brain. Once trauma occurs calcium channels are disrupted, and the leaking calcium and abnormal, injured calcium channels contribute to further damage.<sup>83</sup>

### Magnesium

Magnesium is a mineral that plays a vital role in mental health and is a cofactor for more than 300 enzymes involved in our body's important biological functions including the brain and nervous system. When a TBI event occurs, studies have shown a rapid drop in magnesium levels in the brains of animals and in the blood levels of humans.<sup>89</sup> A drop in magnesium levels induces the production of cytokines, particularly TNF alpha triggering AMPA receptor rendering the cell much more sensitive to excitatory activation leading to a worse prognosis. Preloading the body with magnesium may be beneficial in the event of a TBI.

Magnesium is also essential in obtaining and maintaining healthy mental and emotional well-being. Magnesium deficiencies have been linked to anxiety and OCD,<sup>90</sup> depression,<sup>91</sup> and ADHD.<sup>92</sup>

### Zinc

Zinc is an essential mineral and a powerful micronutrient for both the body and the brain. As a cofactor to several vitamins, it is involved in orchestrating numerous physiological and mental functions.<sup>93</sup> Specific to the brain, zinc works with vitamin B6 (see above) to ensure proper function of neurotransmitters. Zinc is also a key component in the hippocampus, which is responsible for thought and memory.<sup>94, 95</sup>

Research suggests zinc supplementation can improve resilience and reduce TBI-associated depression and improve cognitive function, specifically spatial learning and memory.<sup>96, 97</sup> As far back as 1986 researchers found that a TBI will result in a drop in serum zinc levels and an increase in urinary zinc loss.<sup>98</sup> Researchers also found that zinc deficiency following a TBI

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increases oxidative damage, depression, and delays healing.<sup>99</sup> In fact, in one study 68 patients were randomly assigned to a zinc supplement group or a control group. One month following the TBI, the control group had a mortality rate of 26% while the zinc-supplemented group was only 12%. More significantly, using the Glasgow Coma Scale scores the supplemented group showed improvement 2 weeks earlier than the control group and the improvement continued throughout the study.<sup>100</sup>

Studies suggest that zinc, when properly used, can have a neuroprotective effect on the brain and can reduce TBI related depression while improving cognitive function following injury.<sup>101</sup> As a modulator of neuronal excitability and a cofactor for powerful antioxidants, studies suggest zinc can help blunt the effect of a TBI.<sup>102, 103</sup>

### Forté Elements Brain Protect™ Supplement

Formulated by licensed physicians, the Forté Elements Brain Protect supplement is specifically designed to support healthy brain function and provide the brain with critical elements based on research and scientific evidence. The elements were carefully selected to coincide with research suggesting a neuroprotective benefit.

Unlike other dietary supplements marketed for brain health, the Forté Elements Brain supplement is a Mediceutical, an emerging category of nutritional support that meets stringent standards of manufacture and evidence-based research. A pioneer in the Mediceutical industry, Forté Elements has defined strict criteria for its nutrient supplementation systems. To be categorized as a Mediceutical, a supplement must:

1. Be formulated to support a specific health condition or situation
2. Contain only pharmaceutical-grade ingredients that are Generally Recognized as Safe (GRAS) and where feasible using non-synthetic ingredients.
3. Contain elements that have been validated by clinical research for the specific health condition or situation, as published in peer-reviewed journals
4. Conform to pharmaceutical-grade dosage standards for the specific health condition or situation
5. Be produced in FDA-compliant manufacturing facilities using pharmaceutical-grade manufacturing practices
6. Product has a Certificate of Analysis available confirming that product ingredients meet the Mediceutical standard and are as listed on the product label.

These rigorous guidelines ensure that all Forté Elements mediceutical supplements offer the right blend of nutrients at the right dose for the specific clinical condition. In the case of Forté Brain Protect, the elements are key vitamins, trace minerals and a superior DHA food source that have been shown to play a role in healthy brain function and supports neuroprotection at dosages that have been deemed safe for long-term use. It is recommended that anyone at risk of TBI use this product continually.

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## Supplement Facts

Serving Size 1 Pack (2 Capsules)  
Servings Per Daily Packet 1

### Amount Per Serving

	% Daily Value*
<b>Vitamin A</b> (Acetate) 750 mcg	83%
<b>Vitamin C</b> (Ascorbate Acid) 900 mg	1000%
<b>Vitamin D</b> (D3 as Cholecalciferol) 10 mcg	67%
<b>Vitamin E</b> (d-Alpha Tocopheryl) 83 mcg	553%
<b>Vitamin K</b> (Fat Soluble) 25 mcg	21%
<b>Thiamine</b> (Vitamin B1) 1.5 mg	125%
<b>Vitamin B6</b> (Pyridoxine) 20 mg	1538%
<b>Folic Acid</b> 800 mcg	200%
<b>Vitamin B12</b> (Methylcobalamim) 500 mcg	8333%
<b>Calcium</b> (as Calcium Carbonate) 20mg	2%
<b>Magnesium</b> (Magnesium Oxide) 100 mg	24%
<b>Zinc</b> (Sulfate) 15 mg	136%
<b>Boron</b> 150 mcg	**

\*Percent Daily Values are based on a 2,000 calorie diet. Your Daily Values may be higher or lower depending on your calorie needs.  
\*\*Daily Value not established.

OTHER INGREDIENTS: GELATIN(CAPSULE), MAGNESIUM STEARATE AND SILICA.

## Nutritional Facts

Serving Size 4 Softgels  
Servings Per Packet 1

### Amount Per Serving

	% Daily Value*
<b>Algae Oil</b> 3,880 mg	**
DHA (Docosahexaenoic Acid) 2000 mg	**

\*Percent Daily Values are based on a 2,000 calorie diet. Your Daily Values may be higher or lower depending on your calorie needs.  
\*\*Daily Value not established.

OTHER INGREDIENTS: GELATIN, GLYCERIN AND PURIFIED WATER

THESE STATEMENTS HAVE NOT BEEN EVALUATED BY THE FDA. THIS PRODUCT IS NOT INTENDED TO DIAGNOSE, TREAT, CURE, OR PREVENT ANY DISEASE





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