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Review Article

Diminished brain resilience syndrome: A modern day neurological pathology of increased susceptibility to mild brain trauma, concussion, and downstream neurodegeneration

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Abstract

The number of sports-related concussions has been steadily rising in recent years. Diminished brain resilience syndrome is a term coined by the lead author to describe a particular physiological state of nutrient functional deficiency and disrupted homeostatic mechanisms leading to increased susceptibility to previously considered innocuous concussion. We discuss how modern day environmental toxicant exposure, along with major changes in our food supply and lifestyle practices, profoundly reduce the bioavailability of neuro-critical nutrients such that the normal processes of homeostatic balance and resilience are no longer functional. Their diminished capacity triggers physiological and biochemical 'work around' processes that result in undesirable downstream consequences. Exposure to certain environmental chemicals, particularly glyphosate, the active ingredient in the herbicide, Roundup®, may disrupt the body's innate switching mechanism, which normally turns off the immune response to brain injury once danger has been removed. Deficiencies in serotonin, due to disruption of the shikimate pathway, may lead to impaired melatonin supply, which reduces the resiliency of the brain through reduced antioxidant capacity and alterations in the cerebrospinal fluid, reducing critical protective buffering mechanisms in impact trauma. Depletion of certain rare minerals, overuse of sunscreen and/or overprotection from sun exposure, as well as overindulgence in heavily processed, nutrient deficient foods, further compromise the brain's resilience. Modifications to lifestyle practices, if widely implemented, could significantly reduce this trend of neurological damage.

Key Words: Chronic traumatic encephalopathy, glyphosate, neurotoxins, postconcussion syndrome, sports-related concussion

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INTRODUCTION

While the number of reported sports-related concussions (SRCs) has been steadily rising over the past decade, prompting increased media and medical attention, the number of children participating in the top five organized team sports (OTS), over the same time period, has actually been declining. This surprising juxtaposition is not limited to the world of sports. Neurological disorders are also disproportionately

increasing, with neurological deaths increasing almost 2-fold, while total mortality rates have been declining.

In this paper, we introduce a new concept of how increasing nutrient functional deficiencies and dysfunctional homeostatic mechanisms are plausibly the central mechanism leading to the epidemic we are witnessing in concussion-related and other neurological damage. The study of physiology has well documented a number of innate regulatory and healing mechanisms in place in the human body to maintain homeostasis and enable physiological resilience. In its natural state, the body should be able to tolerate disturbances and withstand shocks without collapse, and to recover quickly from injury or illness. Research has identified, however, that a number of these innate resilience mechanisms and processes are nutrient-dependent and/or are particularly vulnerable to the effects of toxicants.

Concussion, as defined by the 3rd International conference on concussion in sport is "a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces".[127] This definition was further expanded upon to include: "temporary impairment of neurological function that heals by itself over time and where neuroimaging normally shows no gross structural changes to the brain as a result of the condition".[156] Furthermore, it was noted that, in the majority of concussions (80-90%), symptoms resolve in a short period of time (7-10 days), although recovery may be longer for children and adolescents.[126] Studies of college football athletes show 90% of concussed players had a resolution of symptoms within 7 days, with a mean average of 3-5 days for recovery.[125] Prolonged symptom recovery of greater than 7 days is considered to be postconcussion syndrome (PCS).[101,123,175] PCS is often associated with prior concussion (i.e., multiple concussions).[68] Most individuals with PCS report resolution of symptoms by 3 months, but some studies have shown that up to 33% of patients have some persistent symptoms for >6 months, and 15% of patients complain of symptoms >12 months postinjury.[20,22,45,123]

Traumatic biomechanical forces can arise from:

- a direct (to the head) or indirect (to the body) impact (e.g. through sports, workplace accidents),
- rapid acceleration or deceleration (e.g. motor vehicle accidents), or
- intense changes in pressure (e.g. blast exposure).[156]

STATISTICS AND TRENDING

The prevalence of concussion, a subset of mild traumatic brain injury (mTBI),[127] has been dramatically increasing over the past decade.[12] Many sources hold that it is unclear if this increase is evolutionary and organic in nature or simply a by-product of increased awareness by the general public, parents, and coaches as to the importance of reporting and proper medical evaluation for players exhibiting symptoms of concussion.[12,149] However, the majority maintain that the increases are due to an increasing number of available sports activities, increasing competitiveness of youth sports, and increasing intensity of practice and play times, as well as the increased awareness and reporting.[134]

It is estimated that concussion, which is more difficult to define than severe TBI, affects some 100-600 per 100,000 people annually.[77] The Centers for Disease Control and Prevention (CDC) estimates that 1.6-3.8 million SRCs occur annually in the United States alone.[64,90,100]

Furthermore, according to the CDC, US emergency departments (EDs) treat an average (estimate) of 173,285 children and adolescents aged birth to 19 years, for sports and recreation related TBI's per year. In a study conducted at Brown University, it was determined that, from 1997 to 2007, emergency room (ER) visits for concussion occurring from OTSs had almost doubled for children aged 8-13 years (from 3946 to 7791), and more than tripled among those youth aged 14-19 (from 7276 to 23,239).[12,139]

According to Michael A. McCrea, executive director of the ProHealth Care Neuroscience Centre and Research Institute in Waukesha, WI, "….some percentage of the increase should be attributed simply to more concussions. It feels evolutionary and seems natural to me that if we saw great speed, strength, and mass-all the requirements for a collision-at the professional level, we naturally saw it trickle down to the collegiate level, and now it is trickling down to the youth sports level."[139]

Of more concern is that, while increases in concussion are well documented,[139] estimates are likely significantly understated, for two primary reasons. First, athletes (a subset of the general population) are well known to under-report any symptoms that may preclude them from returning to play[168] and, second, statistics (specifically CDC data) are not available for non-ED visits for SRC, which include primary care and specialist office visits, because the brain injury data are easier to collect and quantify in ED patients.[168] Factoring in the tendency of under-reporting by athletes and the exclusion of non-ED visits related to SRC, it is reasonable to project the actual increase of concussion to be of almost epidemic proportion.

A COMPELLING PARALLEL TREND

Genetically modified foods, and the use of pesticides and herbicides, most specifically glyphosate, the active ingredient of Monsanto's Roundup®, have been steadily increasing since the 1990s. In fact, according to data from the USDA: National Agricultural Statistics Service (NASS), and in contrast to claims made by the chemical industries, glyphosate use increased 6504% from 1991 to

2010.[194] These increases are due in part to the emergence of glyphosate-resistant weed populations consequential to the widespread adoption of "Roundup-Ready" GMO corn, soy, alfalfa, canola oil, and sugar beets. Furthermore, the growing popularity of the practice of desiccating wheat and sugar cane, among other crops, just prior to the harvest, is likely to result in an increased residue of glyphosate in foods derived from these core crops,[48] and this may account for the recent epidemic in gluten intolerance and celiac disease,[172] both of which have strong linkages to and impact on nutrient absorption, utilization, and ultimately deficiency.

Despite being strongly discounted by Monsanto, there are mounting good-quality scientific studies that demonstrate negative effects of glyphosate on gut homeostasis, such as reductions in beneficial gut bacteria like Lactobacilli,[186] and enhanced growth of pathogenic microbes such as Clostridium and Salmonella[186] and aflatoxin-producing fungi,[15] to name a few. As we will discuss later, there is an intimate connection between gut health and brain health through the gut-brain axis,[140] and this could explain increased sensitivity to brain trauma.

A MISTAKEN ASSUMPTION

As noted earlier, most mainstream authorities in the field of SRCs maintain that the increase in concussion rates is largely due to the increased awareness and reporting, as well as increased availability of sports activities. However, as Figure 1 indicates, this assumption is mistaken. Lisa Bakhos *et al.*[12] acknowledge this in their article, saying "What is more striking is that the number of SRCs in OTS have increased significantly during a 10-year period despite an overall decline in participation." What we see is an alarming increase in concussions (and neurological-related deaths) that is

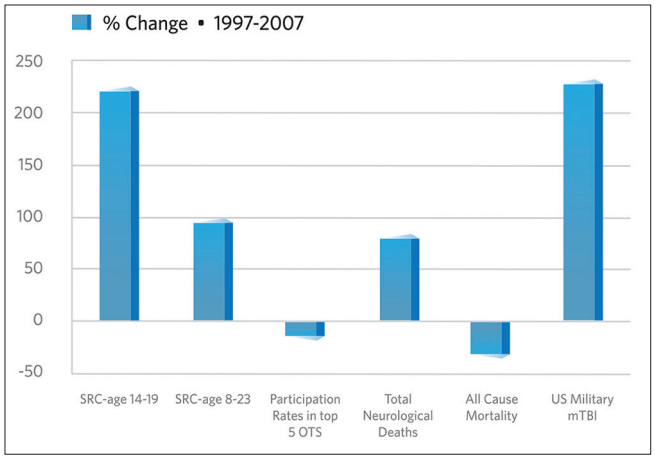

Figure 1: Trends in Concussion (Thionetic Nutrition) SRC = Sports Related Concussion; OTS = Organized Team Sports; TBI = traumatic brain injury. (Data gathered from Bakhos et *al.*,[12] Pritchard et *al.*,[160] and The Defense and Veterans Brain Injury Center website, www.dvbic.org[50])

disproportionate to, or even in a reverse trend to, the number of sports participants. Furthermore, neurological deaths are increasing disproportionally to total mortality rates. Concussion rates are also increasing within the US Military, but not in the way one would expect with active wartime deployments. Over a 10-year period (2000-2010) the rates of total mTBI diagnoses from the Department of Defense increased 233%; while other classifications of brain injury (moderate, severe, penetrating, or unclassified), saw minimal change (www.dvbic.org).

We suggest that, at its core, this downward spiral of neurological demise reflects the inability of the body to maintain homeostatic balance of regulatory and healing mechanisms needed for brain resilience. We postulate that modern day environmental toxicant exposure, along with major changes in our food supply and lifestyle practices, has had a profound impact on the body's ability to absorb and utilize nutrients critical for brain health. Furthermore, we propose that these factors are markedly altering the body's natural state such that neuro-critical nutrients are so depleted and/or functionally deficient that the normal processes of homeostatic balance and resilience are no longer functional. At best, they are operating in a severely diminished capacity, which triggers physiological and biochemical 'work around' processes, resulting in undesirable downstream consequences.

This altered natural state is manifested 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.

We believe that this altered state profoundly affects the body's ability to heal spontaneously from brain injury or assault, whether innocuous or traumatic.

We propose that, over the past decade, these lifestyle and environmental changes have resulted in profound,

yet often unidentified, functional deficiencies of various nutrients within the body. For instance, deficiencies in important minerals such as magnesium and zinc prevent engagement of normal protective and control mechanisms of excitotoxicity. Changes in accessible substrates likely set off a complex 'work around' process, which the body initiates as a fail-safe back-up in reaction to brain injury, but which creates undesirable by-products and downstream consequences, such as increased amyloid-β peptide/plaque (glucose metabolism work around) or encephalopathy (sulfur deficiency).

UNDERSTANDING THE INNATE BRAIN MECHANISMS INVOLVED IN BRAIN INJURY AND DEGENERATION

Before we can present our theory of altered physiology, as it pertains to modern day concussion, it is useful to understand the now currently accepted view of concussion pathophysiology, sequelae, and the underpinning brain mechanisms in play.

Over the past several decades there has been an explosion of research and evolving concepts on the innate mechanisms of the brain at a cellular level. This scientific exploration has essentially shifted the focus of concussions from a more crude structural and anatomical view to a more precise awareness of the biochemical properties involved. The foundational work of Blaylock in the field of brain immunity, excitatory response and immunoexcitotoxicty[25-30] cannot be understated as it laid the scientific groundwork from which to explore this new phenomenon of diminished brain resilience (DBR) syndrome.

Of particular relevance to the issue of modern day concussion, and more specifically DBR Syndrome, is the work of Blaylock and Maroon presented in 2012, which brought to light the awareness that a number of stimuli may interfere with the microglial switching mechanism including occult infections, exposure to neurotoxic metals and pesticides/herbicides, as well as their work outlining the impact of metal toxicity (especially aluminum), documenting that aluminum toxicity is mostly due to its enhancement of excitotoxicity by immune system mediators, via crosstalk between cytokine receptors and glutamate receptors.[27]

PATHOPHYSIOLOGY OF CONCUSSION

Many studies indicate that "rotational forces seem to be a prerequisite for producing the diffuse damage in the brain that underlies the signs and symptoms associated with a concussion."[80] Strong rotational forces cause stretching and shearing of axonal and cell membranes (i.e., diffuse damage), which leads to an unchecked flux of ions through formerly regulated channels and membranes.[56]

However, Blaylock and Maroon[25] present that, with mild injury, most of the initial damage to the axons was not anatomical shearing, but rather involved a progressive degenerative process with any severing of the axons occurring as a secondary event. That is, most of the axonal damage was neurodegenerative and not mechanical.[25,36] As well, acceleration/deceleration and rotational injuries have been shown to trigger rapid intrinsic induction of immune factors, including pro- and anti-inflammatory cytokines, chemokines, interferons, nitric oxide (NO), prostaglandins, and a number of trophic molecules.[4,43,63,73,79,142,179] Some studies indicate that this reaction can occur within 1 h of impact and may continue for a prolonged period. A highly significant excitotoxin, about which we will have more to say later, is glutamate. In uncomplicated minor single concussions, the glutamate is removed by intrinsic brain mechanisms, primarily through glutamate transport proteins, within 24-72 h.[210,223] The same is true for the release of immune factors, with somewhat longer retention, even up to a month following injury.[96,121,191]

Furthermore, as noted by Shipley,[189] "the key to understanding the mechanism of diffuse axonal injury (DAI) lies in the varying densities of brain tissue. Gray matter (primarily the cerebral hemispheres) is less dense than white matter (i.e., the brainstem and central brain structures). Due to different inertial characteristics based on these densities, as the brain rotates during acceleration-deceleration events, lower density tissues move more rapidly than those of greater density. This velocity difference causes shearing of neuronal axons, which connect between the gray and white matter, and explains why DIA lesions are seen most frequently in the areas of the brain where white and gray matter meet."

In the following section, we will develop our hypothesis for the mechanisms by which the brain protects itself from, and heals following, sudden impact damage. However, we need to introduce early the key argument that is foundational to our hypothesis, which centers on the critical molecules, DHA and cholesterol sulfate (CS). DHA is the most abundant omega-3 fatty acid in the brain and retina,[46] and it has an ancient lineage related to photoreceptors.[47] There is an association between a high presence of CS in plasma membranes and a high concentration of DHA.[177] Because CS is more polar than cholesterol due to its sulfate moiety, it extends further into the aqueous environment surrounding the membrane bilayer, which allows its tetracyclic ring system to fit snugly into the pocket of DHA, in direct contrast to unsulfated cholesterol. The sulfate anion attached in this way directly to the membrane complex can produce a protective gelled region of "structured water" surrounding the DHA, where electrons activated by light can be trapped and then directed towards the zinc-containing cavity of an endothelial nitric oxide synthase (eNOS) or a neuronal NOS (nNOS) molecule, attached to the

membrane at the lipid raft. Seneff *et al*.[181] have argued that sunlight induces the synthesis of sulfate by eNOS through such mechanisms, based on the similarity of the eNOS molecular structure to sulfate-synthesizing enzymes in microbes. This allows cholesterol to be sulfoconjugated to renew CS supplies. If these arguments are valid, then the ability to synthesize additional sulfate depends upon an adequate supply of CS as well as DHA. Thus, disruption of the supply of sulfate, as well as cholesterol and the essential omega-3 fatty acid, DHA, has a cascade effect, including changes in the density of the aqueous environment and subsequently increased vulnerability to sudden impact and/or rotational forces.

In summary, there are a few salient points to remember with respect to the pathophysiology of concussions. First, while rotational forces are known to be a prerequisite for the diffuse damage that underlies the signs and symptoms of concussion, in mild injury, most of the axonal damage is now thought to occur from a secondary event that is neurodegenerative in nature rather than mechanical. Second, it is recognized that, with unaltered physiology, uncomplicated, single concussions typically spontaneously heal within 24-72 h via intrinsic brain mechanisms. These intrinsic brain mechanisms interact with specific nutrients as control mechanisms involved with the release of immune factors and excitatory neurotransmitters post injury.

SEQUELAE OF CONCUSSION

Some individuals suffering from mild traumatic brain injuries, especially repetitive mild concussions, are thought to develop a slowly progressive encephalopathy characterized by a number of neuropathological elements shared with various neurodegenerative diseases.[25] Many of these elements resemble some of the pathologic changes seen with Alzheimer's neurodegeneration (Alzheimer's disease; AD), including abundant widespread tau deposits, while some cases demonstrated no amyloid deposits and few neurofibrillary tangles (NFTs).[131,154] The hyperphosphorylated tau seen in CTE is identical to that associated with AD.[131] An experiment using an AD mouse model involved exposing 3 × Tg AD mice to controlled cortical impact injury and measuring the amount of Aβ accumulation postinjury.[214] TBI rapidly increased the levels of both soluble and insoluble Aβ40 and Aβ42 in the injured cortex. The study's authors proposed that chronic accumulation of Aβ following impact injury may increase the risk of developing AD in later life. Subsequent studies have demonstrated two basic patterns of chronic pathology in CTE, one with abundant diffuse amyloid plaques and hyperphosphorylated tau and another essentially devoid of amyloid plaque, but having abundant tau.[131] About half of CTE patients lack significant amyloid plaque accumulation.[25] The presence of apolipoprotein E (APOE) genotypes, in particular APOE4 allele or other unique constitutional patterns, may explain the difference in the two pathological presentations.[87]

While the final pathological manifestation closely resembles that of sporadic AD, there are some differences, especially the predominance of tau pathology over amyloid accumulation in affected regions of the brain. According to Blaylock and Maroon,[25] these anatomical differences in the distribution of pathology can be explained by the diffuse nature of TBI versus a spontaneous development as with AD. Several studies have shown that high levels of glutamate and quinolinic acid (QUIN) increase the deposition of hyperphosphorylated tau protein, resulting in the observed NFT accumulation. Hyperphosphorylation of tau disrupts microtubules, leading to neurodegeneration and memory loss.[86]

IMMUNOEXCITOTOXICITY: FROM CONCUSSION TO CTE

While a central pathological mechanism explaining the development of progressive neurodegeneration (in the subset of individuals who develop slowly progressive encephalopathy after repetitive mild concussions) has yet to be fully elucidated or accepted, a number of studies indicate that a process called immunoexcitotoxicity may be playing a central role in both neurodegenerative diseases as well as CTE. The term immunoexcitotoxicity, originally coined to explain the evolving pathological and neurodevelopmental changes in autism and in the Gulf War Syndrome, refers to the process whereby the interaction between immune receptors within the central nervous system (CNS) and excitatory glutamate receptors trigger a series of events, such as extensive reactive oxygen species (ROS)/reactive nitrogen species generation, accumulation of lipid peroxidation products, and prostaglandin activation. This then leads to dendrite retraction, synaptic injury, damage to microtubules, and mitochondrial suppression.[25] We propose that a number of critical components of our modern environment materially influence the response and modulation of the intrinsic nature of both the immune response and excitotoxicity parts of the immunoexcitotoxicity equation/process, as will be explained later.

A BIOCHEMICAL CASCADE

Glutamate is the most abundant neurotransmitter in the brain,[25] and it is also an important source of energy, when processed by the mitochondria. Glutamate receptor-controlled calcium channels cause the excitatory response through uncontrolled entry of calcium into the neuron. Calcium activates apoptosis through cell death signaling pathways. Abnormal intracellular calcium

homeostasis plays a major role in excitotoxicity, and it appears to be linked to the mechanism associated with amyloid β toxicity.[7,58] White matter secondary injury through this mechanism has a major impact on quality of life for patients suffering from TBI.[155] Different densities between gray/white matter contribute to axonal injury, mostly from a secondary, neurodegenerative process involving rapid response from immune factors and excitatory neurotransmitters and which influence the severity and outcome of mild concussion injury.

Magnesium efflux from mitochondria follows calcium uptake.[188] A drop in magnesium induces the production of cytokines, particularly tumor necrosis factor α (TNF-α), which triggers calcium-permeable α-amino -3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking to the synaptic membrane, rendering the cell much more sensitive to excitatory activation.[105] A rapid and sustained fall in magnesium levels in the brain indicates a significantly worse prognosis.

Microglia, the major immune cells of the brain, not only are intimately involved with the process of excitotoxicity, but also act as mediators in an inflammatory cascade that accompanies brain trauma. Recent studies have pinpointed the activation of the brain's microglia as an early and primary event in traumatic brain injuries. Proinflammatory immune cytokine receptors interact with glutamate receptors in complex ways. Intracellular messengers, including calcium, cyclic AMP, and ROS, respond to both ionotropic and metabotropic glutamate receptors to initiate multiple signaling cascades.[135,148] Immunoexcitotoxicity is a central mechanism in neurological disorders such as Parkinson's disease, AD, stroke, concussion, Posttraumatic Stress Disorder (PTSD), hypoxia/ischemia and brain edema. Prolonged, intense microglial activation is essential to immunoexcitotoxicity.[24]

Microglia, the resident macrophages of the brain, play an important role in mediating the inflammatory response. They respond rapidly to disturbances in homeostasis, and it is the induction of proinflammatory cytokines in response to excitotoxins that leads to neurodegeneration. Three basic states of microglial activation have been proposed: Neurotrophic/phagocytic (ramified/resting/inactive); intermediate (primed); and predominantly neurodestructive (fully activated).[34] Glutamate toxicity is significantly enhanced when it is combined with lipopolysaccharide (LPS) or proinflammatory cytokines.[61]

LPS is a toxic by-product present in gut dysbiosis. Dysbiosis is a state of imbalance between pathological and beneficial gut bacteria. It is a common condition and is brought on by many modern day triggers such as antibiotics and environmental toxicant exposure (beneficial gut bacteria are preferentially vulnerable to pesticides and herbicides), as well as poor dietary choices such as high sugar diets and overconsumption of processed foods. We propose that both exposure to environmental toxins, as well as the resulting dysbiosis, are potent catalysts to a state of persistent immune stimulation within the brain.

Microglia can become "primed" in response to exposure to a number of environmental toxicants, as well as in response to immune stimulation, LPS, ischemia or hypoxia, and brain trauma.[107,109] For example, in an *in vitro* model of Parkinson's disease, dopaminergic neurons, grown in culture with microglia, were exposed to the pesticide, rotenone, and this induced expression of the proinflammatory cytokine, interferon-γ (IFNγ) by the microglia, resulting in neuronal damage.[143]

Primed microglia release much higher concentrations of inflammatory cytokines and excitotoxins, such as glutamate, aspartate, and QUIN, in response to insults, resulting in much greater injury to the soma, the dendrites and the synaptic connections. Thus, even a mild concussion might result in a neurodestructive cascade in the context of previously primed microglia,[25] as schematized in Figure 2.

We suggest that this secondary event manifested as a neurodegenerative state, as noted by Blaylock and Maroon,[25] is responsible for most axonal damage seen in mTBI and concussion and downstream neurodegeneration.

MECHANISMS OF BRAIN PROTECTION/ HOMEOSTATIC BALANCE

The body has a number of innate regulatory and healing mechanisms and processes in place to maintain homeostasis

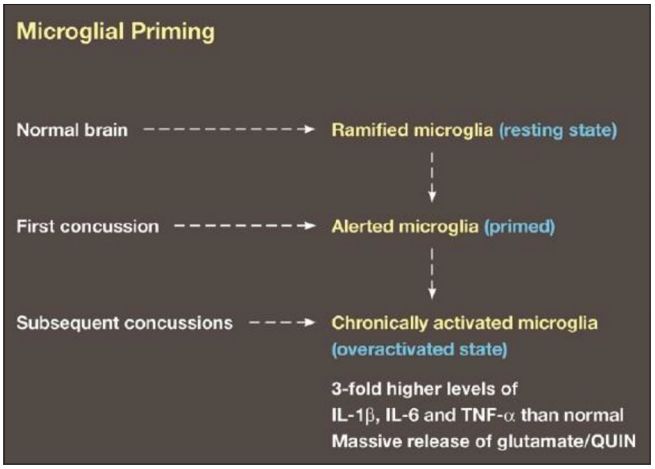

Figure 2: Diagram demonstrating the conversion of a resting microglia in the uninjured brain to a primed microglia with an initial injury. Subsequent injuries, even separated by prolonged periods, can then trigger a hyper-reaction by the fully activated microglia. This in turn results in a more intense immunoexcitotoxic reaction (reprinted from Blaylock and Maroon[25] with permission through an Open Commons license)

and enable physiological resilience, most of which are vulnerable to nutritional deficiencies and environmental toxicants. One such mechanism is a switching mechanism, which normally shuts off microglial activation, once the danger has been contained. Although not fully understood, it involves interactions with various cytokines and fractalkines, all of which reduce microglial activation and downregulate the release of proinflammatory cytokines.[113,114] As well, the brain has a number of mechanisms to restore glutamate homeostasis. These include glutamate transporter proteins, the cysteine/glutamate antiporter system, glutamine synthetase, glutamic acid decarboxylase, and glutamic acid dehydrogenase. Under conditions of oxidative stress, astrocytes release glutamate into the extraneuronal space, thus worsening excitotoxicity.[66] However, we argue here that this response is likely essential for solving a critical problem in sulfate deficiency in the brain.

In neurodegenerative conditions such as AD, abnormalities in many stages of the glutamate cycles have occurred, leading to increased levels of glutamate in the extracellular space outside of the synapse, suggesting that glutamate clearance may be impaired in patients with AD.[164] Neurons in the AD brain are chronically exposed to excessive amounts of glutamate as well as hydrogen peroxide and hydroxyl radicals due to mitochondrial defects.[183] With the suggestion that concussion follows a similar pathophysiological process as AD, the same would likely apply in concussion. It is likely that a combination of reduced glutamate clearance from the synaptic cleft, increased release of glutamate from neurons and glia, and the subsequent activation of the glutamate receptors, all contribute to toxicity mediated by amyloid β-related peptides.[164] As described by Gouix *et al.*,[66] this sets the stage for reverse glutamate transport and tangibly explains the linear path from nutrient deficiency to increased excitotoxicity.

Here, we introduce a novel concept that the pineal gland, a tiny gland in the center of the brain, appears central to the pathology associated with PCS and related conditions, most critically with impact trauma. Specifically, deficiencies in heparan sulfate (HS) dramatically impair the buffering ability of the brain against impact injury due to insufficiently gelled water in the cerebrospinal fluid (CSF). We argue that the pineal gland responds to light stimuli by producing sulfate, and that the sulfate, conjugated to melatonin, is distributed throughout the brain via the CSF. Sulfate plays a critical role in buffering the brain against physical impact, and in degrading and recycling damaged proteins and mitochondria. The pineal gland is outside of the blood–brain barrier (BBB), and it is profusely supplied with blood, second only to the kidney. This makes it vulnerable to exposure to environmental toxicants. Thus, impaired sulfate supply, due to impaired function of the pineal gland, might explain the increased sensitivity to concussion and inability to recover from concussion observed in modern times.

In the remainder of this section, we will develop the argument that PCS can be characterized mainly as a response to deficiencies in sulfate and glutathione (GSH) in the brain, both of which are sulfur-containing molecules. We first discuss the role of heparan sulfate proteoglycans (HSPGs) in neuronal healing, followed by a discussion of their role in protection from impact injury. We then show the role of sleep in clearing cellular debris, an essential function following trauma. Next, we discuss how the pineal gland, through release of melatonin sulfate at night, normally resupplies sulfate to the brain. We propose that the chronic low-grade inflammatory state characterized by PCS is a mechanism to replenish sulfate levels in the brain. After showing how melatonin is integrally connected to GSH up-regulation, thus restoring protective mechanisms in the face of oxidizing agents, we discuss the proposed role of DHA working in concert with CS to catalyze the synthesis of sulfate in the pineal gland in response to sunlight.

HEPARAN SULFATE AND NEURONAL HEALING

HSPGs, attached to the exterior side of membrane-bound proteins in most cells, have profound effects at the cellular, tissue, and organismal level.[174] HS is involved in cell–cell adhesion, cell–matrix adhesion, cell proliferation, lipoprotein metabolism, blood coagulation, inflammation, tissue regeneration, tumor progression and invasion, and bacterial and viral infection, among others.[94] It is through attachment to the negatively charged sulfates of the HSPGs in the extracellular matrix or adhering to the embedded membrane proteins that signaling molecules such as growth factors gain access to the cellular machinery that implements the signaling cascade.[59]

Cerebroglycan is a glycophosphatidylinositol- (GPI)-anchored glypican that is unique to neurons during development.[82,192] It is first expressed immediately following mitosis, and expression continues while the newly differentiated neuron migrates to its final destination and matures. It is also expressed in growing axons of neurons that have reached their final destination. It is highly expressed in the developing brain prenatally and immediately postnatally. Binding to HSPGs likely guides migration of both the neuron and the axon. Thus, HS plays an essential role in neuron maturation and axon growth during development.

It had long been believed that neurons have a limited capacity for regeneration. However, this concept has been dispelled by experimental evidence that neuronal tissues in the hippocampus harbor progenitor stem cells that can differentiate into functioning pyramidal neurons and that they do so in massive numbers when neurons have been damaged through ischemia.[147] These authors proposed, as a strategy for recovery from neurological

injury: "If dormant capacities of endogenous progenitors could be activated by certain manipulations, they may be recruited to generate new functional neurons and repair the damaged CNS." External treatment with growth factors can enhance the healing process. The response of stem cells to shear stress is mediated by HSPGs, and a signaling cascade, launched by growth factors, induces the first step toward differentiation. Depletion of the sulfates in the HSPGs impairs this process.[201]

Because HS participates in neurite outgrowth,[91,97,98] its impaired sulfation would delay recovery from injury. Midkine (MK) is a growth factor that binds strongly to highly sulfated glycosaminoglycan (GAG) units such as heparin and HS, inducing neurite outgrowth, survival, and migration.[225] Desulfation of the trisulfated structure of HS chains bound to syndecans in neuronal cell culture substantially reduced binding affinity. Desulfation of any of the three sulfate groups from heparin also dramatically reduced its MK-binding activity.[88] Extracellular matrix protein synthesis is induced in response to brain injury.[33] Thus, these HSPGs place high demand on sulfate bioavailability and delivery in order to promote recovery from injury.

A ROLE FOR SULFATES IN LOAD RESISTANCE

The glycocalyx is a negatively charged complex network of proteoglycans, glycoproteins, and glycolipids that decorates the plasma membrane of most cells.[207] The GAGs in the matrix are sulfated in an irregular pattern, and the health of the glycocalyx lining the vasculature depends on adequate sulfate content.[41] Responses of cells to signaling molecules become impaired when sulfate is depleted in the extracellular matrix.[144] The sulfated lipids are known as sulfatides, and they are prominent in the myelin sheath.[85] Sulfatides have been found to be severely depleted in Alzheimer's brains postmortem, even in the early stages.[69] This clearly suggests that impaired sulfate supply is a factor in AD.

Sulfation, the last step in the synthesis of GAGs, consumes two ATP molecules for every sulfate ion attached to the GAG chain. There must be something highly significant about the need for such sulfation, given its costly energy requirements. Haskin *et al*.[71] proposed that an important purpose for sulfation can be found by considering the unusual property of sulfate anions to preferentially attach to potassium counterions rather than sodium, the preferred ion for both phosphates and carbonates. The result is a significant dewetting of the GAG molecule, resulting in significantly less water adhering to the extracellular matrix; that is, a smaller fluid/solid ratio. These authors explained as follows: "Areas with a larger fluid/solid ratio would undergo greater deformations in response to compressive loading and larger volumes of fluid would be forced in and out of the tissue during loading cycles. This would likely result in greater matrix destruction in areas with higher water content."[71]

We propose that the same concept applies in the brain; specifically, in the ventricular system that houses the CSF. The ependyma is the thin epithelial membrane that lines the ventricular system of the brain and spinal cord, part of whose role is to produce CSF. It has a thick glycocalyx, extending into the ventricular fluid area, which is likely to provide mechanical buffering to the delicate brain tissues.[165] The ventricles normally contain significant amounts of HS. A mouse model of autism revealed ventricle wall reduction and loss of HSs,[133] and postmortem analyses of brains of individuals with autism have also revealed a reduced amount of HS in the ventricles compared with normal age-matched controls.[157] It was proposed that aberrant extracellular matrix GAG function in the subventricular zone of the lateral ventricles is a potential biomarker for autism.

THE IMPORTANCE OF SLEEP AND METABOLIC CLEARANCE

In a recent study, Xie *et al*.[222] reported that sleep has a critical function in ensuring metabolic homeostasis, and that the restorative function of sleep may be a consequence of the enhanced removal of potentially neurotoxic waste products that accumulate in the awake CNS. This includes the amyloid-β plaque associated with Alzheimer's and brain trauma. Sulfate plays an important role in the lysosome in providing the acidic environment (i.e., sulfuric acid) that promotes digestion of misfolded proteins, so sulfate impairment could easily lead to impaired lysosomal activities, another hallmark of AD.[166]

Neurodegenerative disorders such as AD and Parkinson's disease disrupt the circadian-pineal system,[221] and this is associated with sleep-wake disturbance[190,196,205] and disrupted melatonin synthesis.[205] Circadian rhythms are also disrupted in association with mood disorders.[6,106] Nocturnal levels of melatonin are decreased in AD,[57,220] as is likely the case with concussion, further impairing clearance of postinjury neurotoxic waste. Disrupted sleep is a common problem reported by those suffering from mTBI and PCS.[158] This has a compounding effect on their inability to heal, as their clearance of postinjury neurotoxic metabolic waste is reduced.

A CRITICAL ROLE FOR THE PINEAL GLAND

The pineal gland is a small endocrine gland situated in the center of the brain behind the optic chiasma. It is responsible for synthesizing melatonin at night, which is distributed to neuronal tissues as melatonin sulfate

via the CSF.[202] The pineal gland is integrally connected to the third ventricle, and melatonin sulfate enters the CSF through the pineal recess at the base of the third ventricle.[202]

Exposure to sunlight induces 3-O sulfation of HS in the pineal gland, catalyzed by HS 3-O-sulfotransferase.[94] This unique daytime activity of the pineal gland, which has access to ultraviolet (UV) rays from the sun via the optic chiasma, and which possesses both eNOS and nNOS, offers significant validation for the hypothesis, proposed in Seneff *et al*.,[181] that eNOS produces sulfate upon catalysis by sunlight. Thus, it can be argued that the pineal gland utilizes eNOS and nNOS to restore supplies of HS by day, which are then broken down during the dark cycle so that melatonin can be conjugated with sulfate and distributed throughout the brain via diffusion in the cerebrovascular fluid of the ventricles. Calcification of the pineal gland, which likely impairs eNOS' ability to synthesize sulfate, is associated with AD.[118]

Not only melatonin, but also serotonin, dopamine, and norepinephrine, three other important neurotransmitters, are all sulfated during transport, and their sulfated forms typically greatly exceed their unsulfated forms in the CSF.[204] Quantitative evidence shows that sulfonation of dopamine and serotonin is a more important phase II metabolism pathway than glucuronidation in the human brain.[193] The brain centers that are responsible for producing these neurotransmitters are all situated in close proximity to the pineal gland, and it is logical that they also replenish their sulfate supplies via the NOS-mediated pineal gland production stimulated by sunlight. mTBI often leads to increased anxiety, and empirical evidence indicates that a high anxiety level is associated with delayed recovery.[141] Anxiety is one of the world's most prevalent psychiatric conditions, and the central serotonin system has been implicated in the pathology.[104] Experiments on knockout mice have demonstrated that the 5HT(2C) receptor subtype is critically involved in regulating behaviors characteristic of anxiety.[74]

Mice engineered with a knockout gene for 3-mercaptopyruvate sulfurtransferase (MST) exhibited increased anxiety along with elevated levels of serotonin in the brain.[146] MST can produce hydrogen sulfide gas, which can subsequently be oxidized to sulfate, so it probably plays an important role in the production of serotonin sulfate and therefore in serotonin transport. Its deficiency would be predicted to result in an accumulation of unsulfated serotonin. This also suggests that it is a deficiency in serotonin *sulfate* rather than a deficiency in serotonin that leads to anxiety, and this could explain contradictory results on the relationship between serotonin and anxiety.

Depigmentation of the substantia nigra is a characteristic feature of Parkinson's disease, and increased depigmentation is associated with a reduced level of dopamine and increased degeneration.[60] The locus coeruleus is the principal site for brain synthesis of norepinephrine, and it is also subject to pigmentation loss in association with neurological degeneration. A study of serial sections of human brainstem determined about a 60% reduction in the number of cells containing dopamine-β-hydroxylase (DBH), the enzyme that converts dopamine to norepinephrine, in association with AD.[81] Pigmentation loss, a direct result of depleted supplies of neuromelanin, would lead to increased sensitivity to damage from UV rays entering the optic chiasma.

An experiment examining the effects of transient global ischemia in the rat brain on extracellular metabolites revealed that dopamine concentrations increased 700-fold immediately following the blockage, and that this level was sustained throughout the duration of ischemia, returning to baseline within 10 min of reperfusion.[11] It is plausible that the intense dopamine synthesis enabled intense sulfate transport to the site of injury as dopamine sulfate.

ENCEPHALOPATHY AS A "WORK-AROUND" MECHANISM TO RENEW SULFATE IN THE BRAIN

The excitotoxic response in the brain to inflammatory agents is a well-orchestrated process associated with encephalopathy (CTE). Seneff *et al*.[182] argued that CTE can be viewed as a mechanism to renew sulfate supplies in the brain consequential to severe depletion. Briefly, it involves a major shift in the way glutamate is utilized in the brain, where it becomes a metabolic source rather than a neurotransmitter. QUIN inhibits glutamine synthetase, which prevents the conversion of glutamate back to glutamine.[67] The conversion of glutamate to α-ketoglutarate (αKG) instead allows it to enter the citric acid cycle beyond complex I, which can then provide fuel for the neurons to replace glucose, whose uptake is impaired due to a "type-III diabetes," which, in turn, is due to impaired complex I function.[211] A similar effect is seen in the metabolic state immediately following brain injury, where the oxidative phosphorylation of glucose is reduced in the brain.[212] In parallel, the level of glucose in the vasculature is regulated downward, and this induces the inflammatory cascade. Astrocytes respond to swelling by releasing taurine, glutamate, and aspartate, all of which provide safe alternative fuels for the neurons.

Highly significant is the activity of astrocytes to extract ammonia from glutamine, producing and releasing glutamate, while using the ammonia to maintain the basic pH of mitochondria. Ammonia can now substitute for taurine in this role, and taurine is freed up for its release and subsequent metabolism to sulfate.

Hypochlorite, released by neutrophils, reacts with taurine to produce taurine chloramine, which serves a dual role of protecting neurons from the toxic effects of hypochlorite and converting taurine to a more reactive form. Fever and seizures that are associated with encephalopathy help activate the reaction. Ultimately, taurine chloramine is metabolized, yielding sulfate, which can then resupply sulfate to the HSPGs. Details can be found in Seneff *et al*.[182]

Thus, while encephalopathy is associated with a high risk of collateral damage to neurons through excitotoxicity, it serves an essential role in boosting sulfate levels in the extracellular matrix, which is required in order to replace damaged neurons with newly differentiated progenitor cells, regain the ability to metabolize glucose as a fuel,[182] promote the breakdown and recycling of cellular debris, and, more generally, to support the maintenance of structured (gelled) water that will protect neurons from damage due to mechanical stress.

IMPORTANCE OF GLUTATHIONE TO THE CENTRAL NERVOUS SYSTEM

The brain is the most energy-consuming organ, and therefore it generates a significant amount of ROS that makes it particularly vulnerable to oxidative stress. GSH, a tripeptide consisting of glutamate, cysteine, and glycine, is a major antioxidant in the brain. GSH synthesis requires two enzymatic steps including ATP. Studies have shown that intracellular GSH is important for limiting oxidative stress-induced neuronal injury.[2] GSH depletion enhances oxidative stress, leading to neuronal degeneration.[3] The severity of GSH depletion or deficiency reflects the degree of pathology in Parkinson's disease.[180] Again, this has material relevance to concussion and DBR syndrome due to the role of oxidative stress and the reversal of glutamate transport. Furthermore, synthesis of GSH is dependent on a properly functioning methylation process, which is nutrient dependent. Methylation is dependent upon B vitamins, which are synthesized by beneficial gut bacteria and therefore are known to be depleted as a result of poor gut health.

The presence of methylenetetrahydrofolate reductase (MTHFR) genotypes, in particular, C677T, or A1298C mutations, directly impact enzymatic activity in the methylation process as well. The methylation process follows a number of enzymatic steps in the process from methionine to cysteine and then to synthesis of GSH. Those with these rare MTHFR genotypes are found to have lower GSH levels, and therefore increased risk to oxidative damage.[83] It is likely that cysteine depletion due to its metabolism to replenish sulfate supplies is also a limiting factor. Consequences of low GSH are particularly important with brain health as outlined throughout this paper.

MELATONIN PROTECTS ASTROCYTES VIA GLUTATHIONE UPREGULATION

Much of the neurotoxicity following brain injury relates to free radical oxidative damage to the delicate fatty acids in neuronal plasma membranes. As we have already discussed, GSH plays an important role in protection from the effects of oxidizing agents like superoxide and hydrogen peroxide. In the CNS, GSH is concentrated mainly within the glial cells,[21] and thus, they play a key role in protecting neurons from oxidation-based neurotoxicity.[120] Melatonin has been shown to protect neurons from free radical damage,[18] mainly through its upregulation of GSH, as well as its innate antioxidant effects. Melatonin stimulates the rate-limiting enzyme in GSH synthesis,[206] thus promoting GSH synthesis. GSH peroxidase activity is also stimulated by melatonin, and this may be the most important mechanism by which it exerts its neuroprotective effects.[16] An important effect of this enzymatic action is to reduce the potent free-radical generator, hydrogen peroxide, to water. Furthermore, astrocytes constantly release GSH into the medium, in part to provide a stable source of thiols for the synthesis of sulfur-containing amino acids by neurons,[213] which can also become a source for sulfate synthesis.

"Reactive astrocytosis" is a term to describe the phenomenon of astrocyte activation subsequential to brain injury. Glial fibrillary acidic protein (GFAP), a marker of reactive astrocytes, is overexpressed at the lesion site in brain injury.[84] An experiment on rats confirmed melatonin's important role in protection from free radical damage in the brain.[17] Rats were subjected to constant light exposure for 3 days to prevent melatonin synthesis, and melatonin was simultaneously administered to half of the rats. A control group had neither light exposure nor melatonin treatment. GFAP was overexpressed in the light-exposed rats, but melatonin was able to completely eliminate the effect of light. Furthermore, GSH was depleted in the light-exposed rats without melatonin, whereas GSH expression was upregulated, even when compared with controls, in the group that received both light exposure and melatonin administration.

THE ROLES OF DHA AND CHOLESTEROL SULFATE IN INDUCING ELECTRON FLOW

Lipid rafts are specialized areas of the plasma membrane that are rich in cholesterol and sphingolipids and that serve as signaling platforms by clustering proteins.[93] The omega-3 fatty acid, DHA, plays an important role in the regulation of lipid raft formation in the plasma membrane.[215] With a 22-carbon backbone and six *cis*-double bonds, DHA is the longest and most highly unsaturated fatty acid occurring naturally in organisms.

Furthermore, it is highly conserved in its role in photoreceptor activity associated with the visual system across cephalopods, fish, amphibian, reptiles, birds, and mammals. This process converts photons to electric current in the form of electron flow. Crawford *et al*.[47] postulated that DHA possesses quantum mechanical properties that achieve this transformation. It captures light in the visible to UV frequency range and uses its energy to excite pi electrons and ultimately release them in a continual stream through a process termed "electron tunneling," as explained in Crawford *et al*.[47]

The pineal gland normally contains substantial amounts of DHA.[173] In a rat model, deficiency in alpha-linolenic acid (a precursor to DHA) led to compensatory higher levels of omega-6 fatty acids in the pineal gland.[224] Furthermore, a decrease in melatonin release in response to adenosine by pinealocytes was observed in rats fed an omega-3 fatty acid-deficient diet.[62] Finally, dietary supplements in DHA increase the excretion of melatonin sulfate in the urine, indicating that synthesis of melatonin depends on adequate DHA.[47] These effects can plausibly be explained by the idea that DHA is essential for light-catalyzed sulfate synthesis by the pineal gland. We propose here, for the first time, that the pineal gland utilizes its NOS isoforms to produce sunlight-catalyzed sulfate from reduced sulfur sources.

Concussive injury to rats induced edema and brain swelling, which was partially alleviated by prior treatment with zinc protoporphyrin (Zn-PP).[208] Zn-PP is a potent inhibitor of guanylyl cyclase. Guanylyl cyclase is activated by NO, whose synthesis by eNOS is induced by calcium uptake. Guanylyl cyclase catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP).[112] This NO-cGMP pathway is involved in the sensitization of pain pathways during inflammatory and neuropathic pain.[178] Since, according to Seneff *et al*.,[181] eNOS depends upon both protoporphyrin-based cobalamin and a zinc atom in the cavity formed between the two monomers for sulfate synthesis, we hypothesize that the supplemented zinc promotes eNOS bioavailability to synthesize sulfate. The incorporation of sulfate into the glycocalyx would then alleviate the edema.

GLYPHOSATE, PROCESSED FOOD AND THEIR IMPACT ON INNATE HOMEOSTATIC AND PROTECTIVE MECHANISMS

It is our view that chronic systemic exposure to environmental toxicants, especially glyphosate, while relatively modern, is a significant catalyst to nutrient functional deficiency, disrupted and dysfunctional homeostatic mechanisms as well as compromised gut health; all aspects that contribute to DBR syndrome. Furthermore, the increased consumption of packaged goods and processed foods, which are laden with GMO sourced ingredients and predominantly use omega-6 oils, further disrupts the ideal omega 3:6 ratio. The resulting relatively low omega-3 intake further reduces the amount of brain-supporting eicosapentaenoic acid (EPA) and more specifically DHA available in the diet.

GLYPHOSATE

Today, glyphosate is the most widely used herbicide on the planet, due in large part to its perceived minimal toxicity and its relatively low cost. This is a very dangerous trend, as there are now enough published studies on the various pathological effects of glyphosate to provide convincing evidence of its negative effects on our health.[38,171,186,199]

Glyphosate is the active ingredient in Roundup®. Glyphosate's claimed mechanism of action in plants is the disruption of the shikimate pathway, which is involved in the synthesis of the essential aromatic amino acids, phenylalanine, tyrosine, and tryptophan.[171] The currently held position that glyphosate is not toxic or harmful to humans is predicated on the fact that this shikimate pathway is absent in animals. However, this pathway is present in gut bacteria, the destruction or disruption of which has significant implications to health. Gut microbiota synthesize vitamins, detoxify xenobiotics, and participate in immune system homeostasis and gastrointestinal tract permeability.[78] However, for our purposes, the most significant effect of glyphosate is the disruption of the synthesis of the aromatic amino acids in both plants and microbes, as these are precursors to all the monoamine neurotransmitters-serotonin, dopamine, melatonin, and norepinephrine, as well as neuromelanin and melanin, the bioactive molecules that afford protection from UV exposure. Serotonin is synthesized almost exclusively in the gut,[162] and it therefore delivers sulfate from the gut to the brain. The pineal gland depends upon melatonin to transport sulfate to neurons. And the locus coeruleus (norepinephrine) and substantia nigra (dopamine) depend on melanin to protect them from UV damage.

Glyphosate has been found to have a striking impact on micronutrients of plants exposed to it. It was determined that, in addition to abnormally low levels of tryptophan, phenylalanine and tyrosine (the three aromatic amino acids), glyphosate-sensitive cells also had 50-65% reduced levels of serine, glycine, and methionine.[145] Recent greenhouse experiments[37] demonstrated that glyphosate application to the root system decreased the levels of calcium, magnesium, iron, and manganese in the seeds of plants. Glyphosate binds to and immobilizes all of these divalent micronutrients, impairing their uptake by the plant. These glyphosate-induced deficiencies would carry over to the food supply, leading to deficiencies in these nutrients in humans who consume glyphosate-exposed crops.

A number of animal studies have shown strong evidence of disruption of gut bacteria by glyphosate.[38,186] One study of particular relevance to AD and CTE is the impact of glyphosate on the opportunistic pathogen and antibiotic-resistant Gram-negative bacterium, *Pseudomonas spp*. *Pseudomonas spp*. can break down glyphosate to produce usable phosphate and carbon for amino acid synthesis, but a toxic by-product of the reaction is formaldehyde.[187] Formaldehyde is neurotoxic-it induces, at low levels, amyloid-like misfolding of tau protein in neurons, forming protein aggregates similar to those observed in association with AD.[151] Furthermore, a genome-wide study of the effect of glyphosate on *Escherichia coli* showed that half of the eight genes encoding ATP synthase were downregulated, suggesting impairment in mitochondrial ATP synthesis. At the same time, genes involved in importing sugars were upregulated, which suggests a switch to anaerobic fermentation, producing pyruvate (a much less efficient solution) rather than oxidizing glucose.[111]

Glyphosate, through its disruption of cytochrome P450 (CYP) enzymes, interferes with several functions in the liver that would ultimately impact the brain. The liver depends upon CYP enzymes to activate vitamin D3, to produce CS and bile acids, and to detoxify other environmental toxins, including pharmaceutical drugs. Furthermore, glyphosate, through its tendency to increase blood viscosity, a property that sulfate also possesses, would interfere with the transport of free sulfate from the gut to the liver, requiring transporters that contain a carbon ring to distribute the negative charge and carry the sulfate anion through the hepatic portal vein. Thus, the toxic phenols produced by the pathogenic gut bacteria serve a useful function in delivering sulfate to the liver, but ultimately damage the liver through their high reactivity. The enzyme that activates vitamin D3, 25-hydroxyvitamin D3 1α-hydroxylase (CYP27B1) is a CYP enzyme, and therefore is subject to suppression by glyphosate.[171] Suppression of this activating enzyme by glyphosate could explain the vitamin D3 deficiency epidemic that now exists in the US.[76] Activated vitamin D plays an important role in the kidney in preventing sulfate wasting,[31] so this could contribute to the sulfate deficiency problem that we believe contributes significantly to concussion. Both the vitamin D receptor (VDR) and CYP27B1 are widely distributed throughout the human adult brain.

ALUMINUM WORKS SYNERGISTICALLY WITH GLYPHOSATE

Microglia and astrocytes are primary sources of immune cytokines and glutamate in the brain and are material factors in immunoexcitotoxity. Evidence is compelling and significant from both *in vitro* and *in vivo* studies that aluminum exposure increases both of these compounds in the brain.[148] Aluminum is shown to be a catalyst that can induce immunoexcitatoxicity through a mechanism, likely involving the increase of TNF-α, which triggers the release of glutamate in the presence of aluminum.

A critical discovery of synergistic effects in relation to immunoexcitatoxicity is also well documented throughout Blaylock's work. There is indisputable evidence that subtoxic compounds such as glutamate, aluminum or LPS,[61] to name a few, on their own do not cause neurological injury *per se*, but in combination become fully neurotoxic, leading to excitotoxic lesions. Illumination of this significant risk has profound implications to concussion, given the level of systemic exposure to such compounds.

Aluminum toxicity is a documented cause of encephalopathy,[203] and aluminum, which is present in antiperspirants, high-sun protection factor (SPF) sunscreens, and antacids, bioaccumulates in the brain. In an analysis of aluminum content in various brain tissues postmortem, aluminum was found to exist in at least twice as high a concentration in the pineal gland compared with any other tissues examined, including the pituitary gland, the cortex, and the cerebellum.[99] Aluminum toxicity is a well-established factor in the pathology of AD.[89]

Aluminum toxicity in the liver leads to a disruption of mitochondrial energy production, a switch to anaerobic metabolism in hepatocytes, the production of excessive amounts of α-ketoglutarate by the liver, and the development of fatty liver.[119] Since severe liver pathology, such as liver failure or hepatitis C infection, is associated with encephalitis and cognitive decline,[209] it is easy to imagine that chronic liver disease induced by aluminum could contribute to impaired ability to recover from brain trauma, even in children and young adults.

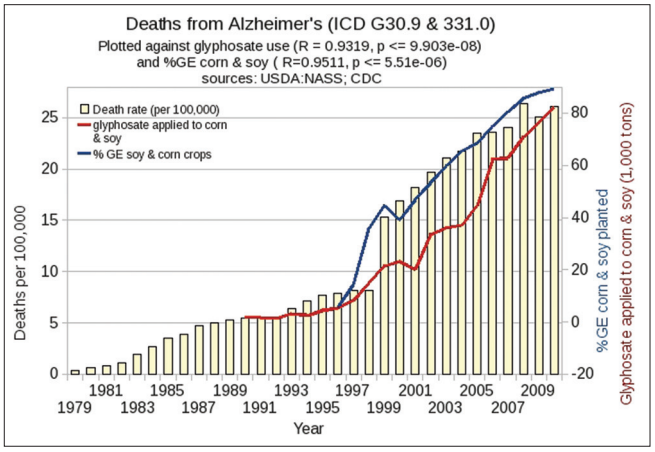

Figure 3: Comparison between the amount of glyphosate applied to corn and soy crops in the US (purple), the percentage of corn and soy that is GMO (red), and the number of deaths from Alzheimer's disease in the US (yellow). Figure reproduced with permission from Swanson[194]

Dietary sources are undoubtedly the biggest contributor to aluminum exposure, but biological mechanisms normally exist to keep all but small amounts of the aluminum from penetrating past the gut barrier. However, citrate is known to facilitate the absorption of aluminum, through its ability to cage aluminum via chelation.[44,92] Glyphosate also cages aluminum through an analogous chemical reaction,[52] and this would be expected to also promote the absorption of aluminum, in the same way. Thus, one of the more alarming possibilities that seems plausible given basic biochemistry is the idea that glyphosate facilitates the penetration of aluminum across the gut barrier.[52] Glyphosate also disrupts beneficial gut bacteria, leading to inflammatory bowel disease and leaky gut, which would further enhance aluminum penetration. Since a common treatment for acid indigestion is an aluminum-containing antacid, there would be a ready supply of aluminum consequential to treatment for the gut dysbiosis induced by glyphosate. Indeed, plasma aluminum levels are elevated in infants consuming high doses of aluminum-containing antacids.[203] Another factor that would enhance encephalopathy in the context of glyphosate is the fact that glyphosate increases the activity of phenylalanine ammonia lyase in exposed cells,[51,75] which could induce excess ammonia production by exposed gut bacteria. Ammonia is strongly implicated in hepatic encephalopathy.[108]

The rates of AD have steadily climbed during the past decade and beyond. In fact, as illustrated in Figure 3, there is a remarkably strong correlation between the amount of glyphosate used on corn and soy crops in the US and the rising death rates due to AD. (Note: The discontinuity between 1998 and 1999 may be partially due to an ICD code change at that time.) This is also correlated with the percent of the corn and soy crop that is engineered to be "Roundup-Ready." Since Alzheimer's is related to PCS via amyloid-β production, it is plausible that glyphosate, perhaps through its ability to promote aluminum uptake, could be an important factor in the increase in this condition as well.

CONSUMPTION OF PACKAGED FOODS AND THE IMPACT ON OMEGA 6:3 RATIO

There is strong documentation as to the antiinflammatory benefits of omega-3 EFAs as well as the pathway of omega-6 EFAs toward a more inflammatory prostaglandin E1 E2 series. Chronic inflammation is increasingly being linked to chronic illnesses. It is viewed that our ancestors' diet included far more fish, seafood, and algae, which leads to a healthier ratio of 4:1 omega 6:3 EFAs diet, and that they experienced reduced chronic illness compared with our modern day Western counterparts. The typical standard American diet (SAD) has a ratio closer to 22:1. This is largely due to the amount of omega-6 polyunsaturated fats from vegetable oils that are used in packaged foods. Omega-3 EFAs are critical for optimal brain health and function. We suggest that the risk to athletes aged 14-19 is pronounced, as this age group tends to consume more processed foods for a number of reasons, and processed foods are laden with GMO sourced ingredients. They also predominantly use omega-6 oils, which further disrupt the ideal omega 6:3 ratio. The relatively low omega-3 intake further reduces the amount of brain-supporting EPA and more specifically DHA available in the diet.

At the same time, our food has become increasingly processed, and there has been a dramatic shift from omega-3 to omega-6 fatty acid consumption. Deficiencies in omega-3 fatty acids, especially DHA, likely also contribute to brain vulnerability, in ways previously outlined.

THE DOWNSTREAM EFFECT: FUNCTIONAL DEFICIENCIES IN CRITICAL NUTRIENTS

Zinc

The white matter abnormalities seen in patients with TBI are strikingly similar to those associated with AD.[55] AD has become an epidemic in the developed countries, but not in the underdeveloped countries.[32] Zinc is the most abundant trace metal in the brain.[216] Patients with AD are zinc deficient compared with age-matched controls.[32,216] A blinded study demonstrated that 6 months of zinc therapy resulted in significant benefits to Alzheimer's patients.[32]

Phytate, found in wheat and nuts, binds to and chelates important minerals such as zinc.[117] Glyphosate is an antibiotic that preferentially kills the bacteria in the gut, Lactobacilli, that produce phytase, an enzyme that breaks down phytate.[186] Glyphosate itself is also an excellent chelating agent, and it has been shown to deplete several minerals in plants.[37] Glyphosate is much more likely to be present in the food in developed countries as compared with developing countries, due to the more widespread adoption of chemical-based agricultural methods.

A recent study on the response of mutant forms of the yeast microbe, *Saccharomyces cerevisiae*, revealed that zinc deficiency activated expression of Tsa1, a "holdase" chaperone that binds to unfolded proteins to prevent them from aggregating.[115] Chaperones are proteins that assist other proteins in folding into their correctly configured active form and protect them from aggregating into misfolded conglomerates like the amyloid-β associated with AD. Zinc deficiency also induces excess production of ROS, through a mechanism that is not understood. We hypothesize that a contributing factor is the requirement of NOS for zinc's presence in the cavity between the two monomers in order to produce sulfate.[181] Impaired sulfate

synthesis would result in the excitotoxic calcium cascade described earlier in this paper. Impaired sulfate supply would also likely induce protein misfolding due to an inability to properly structure the water in the cytoplasm.[185]

Inflammation plays a fundamental role in the pathogenesis of AD, and it is believed to be a powerful pathogenic force. Amyloid-β oligomers and fibrils have been labeled as "danger-associated molecular patterns" (DAMPs), due to their ability to activate a wide array of pattern recognition receptors such as toll-like, (NOD)-like, formyl peptide, Receptor for Advanced Glycation Endproducts (RAGE), and scavenger receptors.[170] Inflammation induces excess superoxide, which is necessary to oxidize the sulfur in homocysteine thiolactone[128] or the sulfur in hydrogen sulfide gas (H_2S) derived from cysteine via cystathione β-synthase (CBS). H_2S, produced in the brain by CBS, functions as a neuromodulator and a smooth muscle relaxant.[53] We hypothesize that H_2S is oxidized to sulfate via sulfite oxidase, which is dependent on the bioavailability of the rare mineral, molybdenite. Not only are AD patients severely deficient in the levels of H_2S in the brain, but also homocysteine accumulates in the serum of AD patients,[53] suggesting a reduced ability to produce sulfate from homocysteine via the pathway described in McCully.[128] Thus, when the synthesis of sulfate via NOS is impaired, alternative methods of sulfate synthesis are induced, which, unfortunately, jeopardize the cell's viability as a consequence of excess exposure to ROS.

Magnesium

Magnesium is one of the most abundant ions in the brain, and it plays a major role in the plethora of biochemical and physiological CNS tissue functions, as well as numerous other processes that affect muscle function, including oxygen uptake, energy production, and electrolyte balance. Magnesium is also essential for lysosomal function. Magnesium activates the formation of microtubule-lysosome complexes,[138] and magnesium is required for the breakdown of the cell walls of ingested bacteria by lysosomes.[103]

Studies suggest that strenuous exercise increases urinary and sweat losses, which may increase magnesium requirements by 10-20%.[152] Furthermore, it has been shown that exercise induces a redistribution of magnesium in the body to accommodate metabolic needs. There is evidence that marginal magnesium deficiency impairs exercise performance and amplifies the negative consequences of strenuous exercise (e.g. oxidative stress). The level of demand and utilization of magnesium has significant implications for athletes, as it is estimated that 90% of athletes are deficient in magnesium compared with the general American population at 68%.[152]

In both humans and animals, low magnesium levels alone can trigger inflammation in a number of tissues, including the brain, as well as lowering seizure thresholds. Since glyphosate has been shown experimentally to reduce the magnesium uptake by soy,[37] it can be anticipated that foods derived from soy exposed to glyphosate would be magnesium deficient. Experimentally, in a rodent model, during progression of magnesium deficiency there is a significant increase in inflammatory cytokines, such as TNF-α among others, within 5 days. TNF-α is a powerful trigger of trafficking GluR2-lacking AMPA receptors (calcium permeable) to the synaptic membrane.[24] This demonstrates that a vital function for CNS magnesium is the modulation of the NMDA glutamate receptor, and that low levels of magnesium can significantly enhance excitotoxic sensitivity.

A study of impact-acceleration brain injury in rats confirmed that intracellular free magnesium concentration experienced a sustained decline for several days following injury, along with a significant neurological deficit, suggesting that repeated administration of magnesium may be necessary following brain trauma.[72] The observed rapid and sustained fall in blood and brain magnesium levels often seen in TBI is associated with significantly worse prognosis in patients who experienced a continued decline in magnesium even when they were corrected within 24 h following injury. Moreover, low magnesium leads to a significant fall in cellular GSH and a dramatic increase in free radical production,[24] the implications of which have been clearly outlined previously.

Omega-3 EFAs

Brain omega-3 EFAs are the most extensively studied fatty acids in the body.[123] Studies have found that omega-3 EFAs can decrease the toxic effects of glutamate, which is released in large amounts after TBI.[136,137,219] Postinjury excessive glutamate causes an influx of calcium, which is attributed to gray and white matter secondary injury.[155] It is believed that omega-3 EFAs may have a suppressive effect on ion channels and prevent cell death.[19]

Studies utilizing rodent models of experimental injury have shown that preinjury dietary supplementation with fish oil effectively reduces posttraumatic elevations in protein oxidation resulting in stabilization of multiple molecular mediators of learning, memory, cellular energy homeostasis, and mitochondrial calcium homeostasis, as well as improving cognitive performance.[218,219] Not only have the benefits of pretraumatic DHA supplementation been independently confirmed,[136] but DHA supplementation has also been shown to significantly reduce the number of swollen, disconnected, and injured axons when administered following TBI.[10,136] Maresins, derived from oxidation of DHA, are potent antiinflammatory agents that promote resolution of the inflammatory response.[184] DHA has provided neuroprotection in experimental models of both focal and diffuse TBI.[159] Furthermore, there is strong evidence that DHA is the most neuroprotective component of

the omega-3 oils and makes up the most abundant fatty acid in neural membranes, especially synapses.[24] We hypothesize that this relates to its unique ability to convert photons into electric current as well as its role in inducing lipid raft formation in the plasma membrane and in catalyzing the synthesis of sulfate by eNOS.

When brain slices from the hippocampus are treated with DHA, but not with EPA, they show remarkably reduced excitotoxicity following AMPA-type glutamate receptor response.[132] Research suggests that abnormal trafficking of calcium-permeable AMPA receptors is strongly linked to brain inflammation. Omega-3 fatty acid deficiency in rats increases the release of proinflammatory cytokines IL-6 and TNF-α and raises C-reactive protein. This study also found significantly greater serotonin metabolism in the frontal cortex, hypothalamus, and ventral striatum, which in the presence of brain inflammation, shifts tryptophan metabolism toward QUIN generation. As stated earlier, QUIN, an excitotoxin, is a potent inducer of the hyperphosphorylation of tau, a critical process in NFT, as well as inducing glutamate release. Deficiencies in DHA increase abnormal amyloid precursor protein (APP) processing, leading to amyloid deposits in the brain. Conversely, supplementation with DHA increases the secretion of soluble amyloid precursor protein (sAPP), which inhibits apoptosis and protects the synapse. DHA, when given prior to injury, also reduces axonal damage in rats subjected to TBI. This would have applications in preventing CTE and possibly ameliorating PCS. Furthermore, studies have shown that supplementation with DHA suppresses microglial activation.

Vitamin D3, dehydroepiandrosterone sulfate, and immunity

The sunscreen industry in the US has grown on average by 4.2% per year during the past two decades, such that it now represents a $1.3 billion industry. The use of sunscreen reduces the body's natural process of vitamin D synthesis. This lifestyle choice contributes significantly to vitamin D deficiencies, which are problematic, especially when it comes to brain health and resilience. Sunscreen also likely interferes with CS synthesis in the skin, particularly since it typically contains both retinoic acid and aluminum, both of which would interfere with the synthesis of sulfate by eNOS.[182]

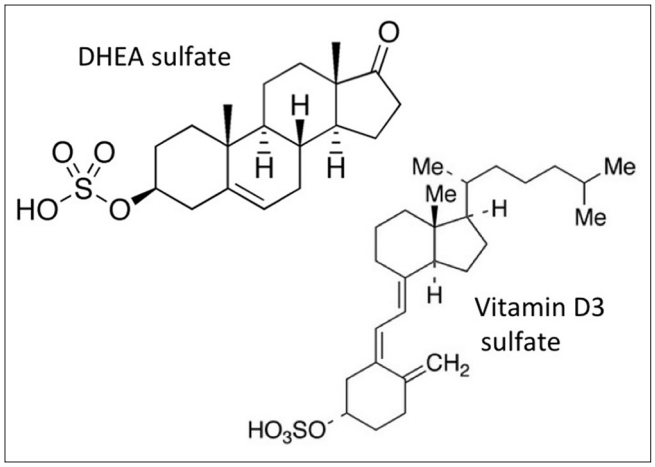

Figure 4: Molecular structure of dehydroepiandosterone sulfate and vitamin D3 sulfate

Vitamin D deficiency is endemic in the adolescent, adult, and elderly populations in the US,[40,65,76,197] and it has been associated with inflammatory, autoimmune, cardiovascular, neuromuscular, and neurodegenerative diseases, as well as cancer.[95,159] Population-based studies have suggested that vitamin D deficiency in the elderly is indeed associated with an increased prevalence of Parkinson's disease,[54] dementia, AD, stroke risk, and higher prevalence of MRI findings suggestive of primary cerebrovascular lesions.[35] Some anecdotal studies suggest that vitamin D may be both neuroprotective and vasculoprotective.[217] More recent research has suggested that vitamin D supplementation and the prevention of vitamin D deficiency may serve valuable roles in the treatment of TBI and may represent an important and necessary neuroprotective adjuvant for post-TBI progesterone therapy.[8,39,40] As mentioned earlier, glyphosate disrupts CYP enzymes, which are needed to activate vitamin D3 by converting it to 25-dihydroxyvitamin D3. Thus, sun exposure is not sufficient to produce functional vitamin D3 when glyphosate disrupts its activation.

Vitamin D exists in a sulfated form, vitamin D3 sulfate [Figure 4], and this form, produced in the skin upon sun exposure, is a major circulating form in humans.[9] Dehydroepiandrosterone (DHEA) sulfate [Figure 4] is the predominant form of DHEA in the blood.[150] DHEA is the main precursor for the sex hormones, and low serum levels of DHEA sulfate are predictive of cardiovascular disease.[200] Hence, both vitamin D3 and DHEA, like the monoamine neurotransmitters, are sulfate transporters. Seneff *et al*.[181] argued that eNOS is a moonlighting enzyme, which produces sulfate from reduced sulfur sources and superoxide, catalyzed by sunlight, when it is attached to the plasma membrane at caveolae. The sulfate anion is then used to conjugate both vitamin D3 and cholesterol. Following calcium uptake, eNOS detaches from the membrane and becomes bound to calmodulin and phosphorylated, activities which then activate NO synthesis by eNOS. Hence, calcium uptake, as in the reaction cascade following brain trauma, suppresses the synthesis of sulfate by eNOS.

A relationship has been proposed between adverse cognitive and behavioral effects and vitamin D deficiency.[124] Intriguingly, schizophrenia is more prevalent among people born in winter months and dark-skinned people living at high latitudes, a clear indicator of protective effects of sunlight exposure.[49,116,130,167] Enlarged

ventricles and a thinner cortex in the brain are observed in association with schizophrenia and also in the brains of rats with restricted vitamin D intake.[70] To us, this suggests insufficient sulfate supply to the CSF as a consequence of impaired delivery of sulfate by vitamin D3 and other sterol and neurotransmitter transporters. Head injury is a risk factor for schizophrenia, especially in males[153] or when there is a familiar genetic predisposition.[1]

Vitamin D3 modulates the immune response, and vitamin D3 deficiency is associated with increased risk to infection.[5] There is substantial evidence that Alzheimer's is related to an increased likelihood of infective agents appearing in the brain. A number of studies have demonstrated significantly more bacteria/infective agents within the brains of Alzheimer's patients than controls, sometimes as high as 17-fold.[183] It has been found that pesticides disrupt BBB permeability, and that neuroinflammation and oxidative stress, factors described within this paper, compromise BBB.[42] We propose that chronic exposure to pesticides, neuroinflammation, and oxidative stress disrupts the integrity of the BBB, allowing bacteria and infective agents easy migration from the bloodstream to the inner sanctum of the brain. Chlamydia pneumoniae is a pathogen that has been found to be frequently present in the core of amyloid-β plaque regions in the Alzheimer's brain.[13] Chlamydia pneumoniae produce a variant of HS using a set of enzymes that are unique to that species,[163] which suggests that their presence in the brain may have a beneficial role in providing HS to the neural tissues.

Polyphenols, flavonoids, and mucopolysaccharides: A sulfate connection

Aside from omega-3 fatty acid supplements, a wide range of natural remedies have been used to treat concussion. These include curcumin, resveratrol, vitamin D, green tea, coffee, vitamin C, and vitamin E.[23,159] Curcumin, resveratrol, vitamin D, and vitamin C all have a sulfated form that is commonly produced for transport in the vasculature. Green tea and coffee, both contain abundant polyphenols and flavonoids that can also serve as sulfate transporters.

Polyphenols and flavonoids have become popular supplements due to their alleged benefits to memory and cognition, although studies have thus far failed to explain the underlying physiological mechanism of their supposed benefit.[176] It is generally observed that only small amounts of these substances are absorbed into the general circulation, and it is questionable whether any makes it into the brain.[23] Samsel and Seneff[171] proposed that their benefit lies mainly in their ability to transport sulfate from the gut to the liver, a role that is urgently needed in the context of glyphosate exposure. Gingko biloba, a medicinal herb, is rich in flavonoids and polyphenols.[198] Stressing rats through forced swimming results in reduced norepinephrine levels in the hypothalamus, which is prevented by simultaneous treatment with gingko biloba.[169] Similarly, supplementation with polyphenol-rich blueberries leads to increased hippocampal plasticity and reverses cognitive and motor deficits.[102] We hypothesize that these benefits are due to the ability of polyphenols to promote sulfate transport. Sulfatases and sulfotransferases in the liver transfer sulfate from polyphenols to cholesterol, to be distributed to all the tissues, including the brain.[171]

Sulfomucopolysaccharide treatment of aging male rats induced reduced dopamine turnover in the nucleus accumbens associated with improvements in learning and memory.[110] This could be due to a replenishment of the supplies of sulfated polysaccharides to the CSF, supplanting the need for dopamine-mediated sulfate transport. Similarly, clinical trials involving treating patients with dementia with GAG polysulfate showed improvements in social function, sensory response, and work performance.[14] Fully sulfated heparin exhibits much greater antioxidant activity than heparin from which the N- and O-sulfate groups have been removed,[166] manifested as reduced peroxidation of linolenic acid. One possibility offered as an explanation is that it induces a highly acidic environment in the lysosome where iron can be oxidized from the +2 to the +3 state while producing water rather than highly reactive hydrogen peroxide as the other reaction product.

Conclusion: Sports-related concussion is a modern day problem prompted by diminished brain resilience.

It is quite evident there is an alarming increase of reported concussion in sport (up to 3-fold in some cases) despite confirmed lower levels of participation rates. This surprising juxtaposition is not limited to the world of sports. Neurological disorders are also disproportionately increasing, with neurological deaths increasing almost 2-fold, while total mortality rates have been declining. In short, more of us are getting sick and dying from neurological disorders and injury.

We believe this phenomenon is a manifestation of increased susceptibility to neurological damage, specifically relatively mild brain trauma, such as concussion, with sometimes devastating long-term degenerative damage, as seen with increasing evidence of CTE in athletes after careers of repetitive sub-concussive episodes.

This susceptibly to neurological damage, in turn, is due, both directly and indirectly, to profound and systemic changes in modern life, including but not limited to long-term pesticide and chemical exposure, reduced exposure to natural sunlight, poor omega 3/6 ratio within the diet (particularly, deficiencies in DHA), insufficient

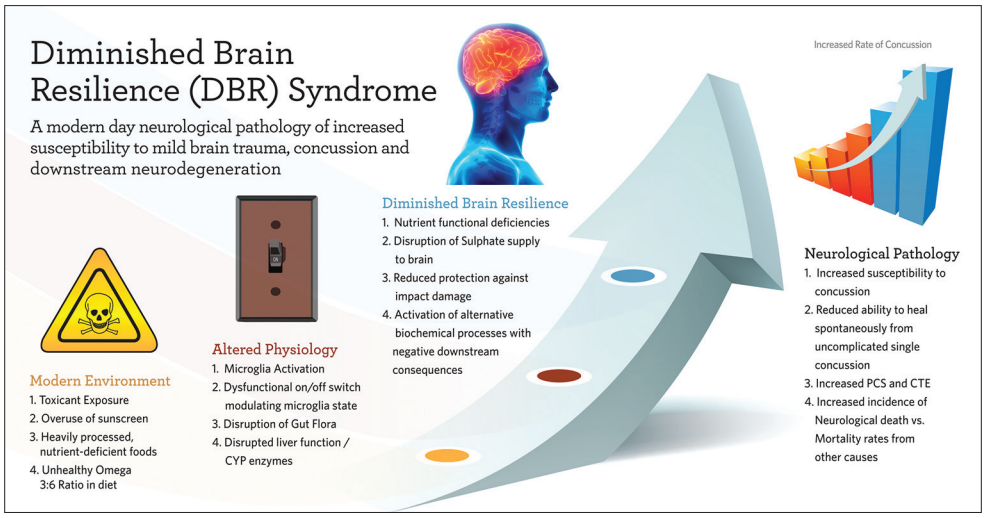

Figure 5: Schematic illustrating the phenomenon of Diminished Brain Resilience

dietary sulfur, and over-consumption of processed foods. We propose that one of the most troubling contributions, which in our opinion is a major catalyst of the altered physiology in humans, is the explosive increase in glyphosate exposure. Glyphosate was first introduced in the US in 1974, and its usage has steadily escalated in the intervening years. We believe that this cumulative exposure results in a systemic depletion in sulfate supplies to the neural tissues, leaving them especially vulnerable to jostling through sudden impact, on account of insufficient water structuring in the CSF. Furthermore, sulfate depletion impairs two important repair mechanisms following injury, neuronal repair through neurite outgrowth and lysosomal recycling of cellular debris.

In this article, we have described a perfect storm of events such as immunoexcitotoxicity, excitotoxicity, and neuroinflammation, and have argued that these are due to exposure to subtoxic substances such as aluminum and LPS that turn fully neurotoxic and neuro-damaging in the presence of a heightened excitatory immune response. This perfect storm of events results in a profoundly reduced bioavailability of neurocritical nutrients such that the normal processes of homeostatic balance and resilience are no longer functional, as summarized in Figure 5.

SEQUELAE OF AN ALTERED FOOD SUPPLY: PESTICIDE EXPOSURE AND INCREASED CONSUMPTION OF PROCESSED FOODS

We propose that the following factors are all implicated as sequelae to DBR syndrome prompted mainly by modern day levels of environmental toxicant exposure, nutrient functional deficiencies, poor gut health, improper balance of omega 3:6 EFAs, and reduced exposure to natural sunlight.

Microglia activation

It is well supported that exposure to pesticides, herbicides, and fungicides activates microglia, shifting the microglia from a resting (ramified) state to an intermediate (primed) state.[122,195] This primed microglia state results in a hyper-response with subsequent brain assaults, no matter how mild.

Interference with the normal switching to the quiescent (ramified) phenotype (the resting state)

Research shows that pesticides interfere with the mechanism that normally switches off the microglia activation when the danger has passed.[129,161] We hypothesize that this is directly related to the impaired supply of sulfate to the neural tissues.

Disruption of gut flora, leading to gut dysbiosis

Gut dysbiosis both disrupts the bioavailability of important nutrients and produces toxic by-products such as LPS and toxic phenols.[171] Some of the sequelae include:

- Increased inflammation and oxidative stress
- Activation of microglia (prompted by presence of LPS)
- Hippocampus and amygdala damage
- Reduced levels of serotonin, dopamine, 5-hydroxytryptamine (5-HTP), melanin, and norepinephrine
- Damage to mitochondria (through oxidative stress)
- Decreased absorption of zinc
- Decreased GSH
- Decreased ability to detoxify toxins via the liver by destruction of CYP enzymes.

Nutrient functional deficiencies

- Magnesium deficiencies linked to increased TNF-α, which triggers the process of calcium dysregulation at the synapses and is instrumental in excitotoxicity

Table 1: Nutritional deficiency and resulting physiological consequences

Functional deficiencies in nutritional compounds	Impact deficiency has on brain resilience
Sulfur	Impaired melatonin supply; impaired recycling of debris; impaired function of DHA in the membrane; increased sensitivity to sudden impact; impairment in neurite outgrowth needed for healing
Magnesium	Lowering of seizure thresholds; significant increase in inflammatory cytokines; reduced modulation of NMDA glutamate receptors leading to enhanced excitotoxic sensitivity; significant fall in cellular glutathione and dramatic increase in free radical generation; significantly worse prognosis in concussion
Zinc	Increased aggregates of misfolded proteins, such as amyloid-β associated with AD and CTE; excess production of reactive oxygen species (ROS)
Omega-3 EFAs, specifically DHA	Increased toxic effects of glutamate; reduced mitochondrial calcium homeostasis; poor cognitive performance; increased number of swollen, disconnected and injured axons; abnormal amyloid precursor protein (APP) processing, leading to amyloid deposits in the brain; reduced suppression of microglial activation
Vitamin D	Increased likelihood of infectious agents in the brain
Aromatic amino acids, polyphenols, flavonoids and mucopolysaccharides	Reduced sulfate transport from the gut to the liver and brain
B-Vitamins, specific to methylation	Reduced glutathione synthesis, resulting in increased oxidative stress; increased homocysteine

DHA: Docosahexaenoic acid, CTE: Chronic traumatic encephalopathy, ROS: Reactive oxygen species, APP: Amyloid precursor protein, NMDA: N-Methyl-D-aspartate, AD: Alzheimer's disease, EFAs: Essential fatty acids

- Deficiencies in omega-3 fatty acids, especially DHA
- Deficiencies in critical nutrients including, but not limited to sulfur, zinc, magnesium, and cobalamin.

Disruption of sulfate supply to the brain

- Interference with synthesis of CS due to its dependence on CYP enzymes
- Disruption of synthesis of aromatic amino acids by plants and by gut bacteria, reducing the bioavailability of the derivative neurotransmitters and hormones that transport sulfate
- Promotion of aluminum toxicity from dietary sources leading to liver impairment
- Interference with transport of free sulfate in the serum due to competitive inhibition by glyphosate, contributing to high blood viscosity.

In Table 1, we have attempted to schematize the downstream consequences of various nutrient functional deficiencies specifically as they relate to brain injury, illness, and resiliency.

CONCLUSION

In summary, we have brought to light a compelling juxtaposition of decreasing participation in the top five OTSs and overall mortality rates, in sharp contrast to increasing rates and incidence of brain injury, specifically SRC, as well as neurological illness and death. This juxtaposition suggests that a more pervasive cause is at play.

Considering the known physiological changes that modern life effects on the human body, and the corresponding increase in neurological injury, illness, and deaths, we suggest that systemic and cumulative exposure to the environmental toxicant, glyphosate, compounded by other lifestyle and dietary changes, is a prominent catalyst of a modern day neurological syndrome, DBR syndrome, currently being manifested in a new type of SRC, PCS, CTE, and other neurological disorders than we have seen historically.

With glyphosate now being detected in our water and air supply, in addition to our food supply and human urine samples, fully eliminating toxic exposure is improbable, thus leading to a state of constant hypersensitivity or susceptibility to mild brain trauma. It is unclear if the physiological damage already caused by glyphosate exposure is reversible, so interventions should be focused on minimizing the damage, prophylactically.

Finally, while a number of recent papers describe promising positive effects of natural nutritional compounds as neuro-protective, translating those promising benefits from preclinical studies to real life has been limited. We argue that simple supplementation may not be enough to achieve the desired benefit if patients are functionally unable to absorb or utilize the supplemented nutrient. More studies are required to determine the optimal levels of nutrients required to maintain neurological resilience in response to SRC and the role that functional deficiencies play in susceptibility to and severity of concussion. Secondary to that, further studies are required to test the effectiveness of various nutritional and lifestyle interventions designed to offset the impact of modern day life on brain resilience, specifically, minimizing glyphosate exposure and its sequelae through the adoption of organic non-GMO foods, improvement of gut health through probiotics, increased consumption of omega-3 fatty acids, especially DHA, dietary enrichment in micronutrients, particularly minerals involved in brain resilience, such as sulfur, zinc, and magnesium, and increased exposure to sunlight.

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