Age Related Cognitive Decline

All aging humans will develop some degree of decline in cognitive capacity, usually including the following symptoms:

- forgetfulness
- decreased ability to maintain focus
- decreased problem solving capacity

If left unchecked, symptoms oftentimes progress into more serious conditions, such as dementia and depression, or even Alzheimer's disease.

Fortunately, proactive lifestyle changes, cognitive training, and nutritional interventions such as **phosphatidylserine** and **glyceryl phosphoryl choline** have been shown to decrease the rate of intellectual decay and potentially reverse age-related cognitive decline.

Causes of Age-Related Cognitive Decline

Many factors contribute to age-related cognitive decline:

- Oxidative stress and free radical damage
- Chronic low-level inflammation
- Declining hormone levels like estrogen, testosterone, DHEA, pregnenolone
- Inner arterial lining (endothelium) dysfunction
- Insulin resistance
- Excess body weight
- Suboptimal nutrition
- Loneliness, lack of social network, and high stress

Dietary and Lifestyle Changes

Several dietary and lifestyle changes can help reduce age-related cognitive decline:

- Switch from a western diet high in simple sugars and saturated fats to a Mediterranean diet high in mono- and polyunsaturated omega-3 fats, fiber, and polyphenols
- Caloric restriction may improve learning and memory
- Cognitive stimulation and training, including playing chess and speaking more than one language, can enhance cognitive reserve and convey protection against loss of brain function
- Exercise is known to increase levels of brain-derived neurotrophic factor, which can lead to enhanced cognitive function
- Moderate alcohol consumption (up to 2 drinks/day) and caffeinated coffee consumption (~3 cups/day) may convey protection against cognitive decline

Integrative Interventions

- **Fish Oil:** Daily omega-3 supplementation was independently associated with a dramatic reduction in cognitive decline over a 1.5-year period in an aging study population.
- **Phosphatidylserine:** Human clinical trials have found that supplementing with phosphatidylserine improves cognitive function in aging subjects with cognitive impairment.
- **Glyceryl Phosphoryl Choline (GPC):** Patients taking GPC showed neurological improvement and relief of clinical symptoms of chronic cerebral deterioration that was superior or equivalent to that obtained with prescription drugs.
- **Acetyl-L-carnitine:** A meta-analysis of data from over 21 studies shows that supplementation with acetyl-L-carnitine improves cognitive deficits observed during aging and pathological brain deterioration.
- **Huperzine A:** Patients with Alzheimer's disease improved their scores on standard cognitive tests after supplementing with huperzine A.

Age Related Cognitive Decline

All aging humans will develop some degree of decline in cognitive capacity as time progresses. Data indicates that deterioration of the biological framework that underlies the ability to think and reason begins as early as the mid twenties and includes a drop in regional brain volume,[1,2,3,4,5] loss of myelin integrity,[6,7] cortical thinning,[8,9] impaired serotonin, acetylcholine, and dopamine receptor binding and signaling,[10,11,12,13] accumulation of neurofibrillary tangles,[14] and altered concentrations of various brain metabolites.[15] Cumulatively these changes give rise to a variety of symptoms associated with aging, such as

forgetfulness, decreased ability to maintain focus, and decreased problem solving capability. If left unchecked, symptoms oftentimes progress into more serious conditions, such as dementia and depression, or even Alzheimer's disease.

Cognitive decline does not affect all individuals equally; clear associations exist between the rate and severity of cognitive decline and a variety of factors, including oxidative stress and free radical damage,[16,17,18] chronic low-level inflammation,[19] declining hormone levels,[20] endothelial dysfunction,[21] excess body weight,[22] suboptimal nutrition,[23] lifestyle,[24] social network,[25] other medical conditions,[26] and various biomarkers.[27] Fortunately, many of these factors are modifiable to a significant extent, and proactive lifestyle changes, cognitive training, and nutritional interventions have been shown to decrease the rate of intellectual decay and potentially reverse age-related cognitive decline.

The Aging Brain

The aging process profoundly impacts the brain in ways that can be observed on multiple levels, ranging from sub-cellularly to macro-structurally. On a diminutive scale, aging causes deterioration of neuronal and mitochondrial membranes, which leads to the loss of cellular integrity and impaired neuronal function.[28,29,30] Steep age-related declines in neurotransmitter synthesis and signaling,[31,32,33] coupled with reductions in synaptic density and plasticity (adaptability),[34,35] and loss of as much as 50% of the length of myelinated axons[36] **(see figure 1)** make the brain increasingly less efficient as we age.

Figure 1: Anatomy of a neuron

In a broader sense, the physical structure of the brain as a whole also deteriorates with age. Shrinkage and death of neurons, and reductions in the number of synaptic spines and functional synapses contribute to annual reductions of as much as 0.5% to 1.0% in cortical thickness (the cortex is the outermost layer of the brain) and sub-cortical volume in some regions of the brain.[37] Specifically, even in healthy individuals, aging accounts for volume variances of 37% in the thalamus, which is involved in sight, hearing, and the sleep-wake cycle; 36% in the nucleus accumbens, which plays a major role in mood regulation (e.g. pleasure, fear, reward); and 33% in the hippocampus, a critical site for consolidation of short-term to long-term memory.[38] Taken together, age related neuroanatomical changes account for an estimated 25% to 100% of the variance in cognitive ability between young and aged individuals.[39] In other words, age related cognitive decline occurs in tandem with the physical degradation of brain structure. Thus, conserving cognitive vigilance into late life requires early and aggressive intervention to preserve the brain in its youthful physical and functional state.

Biological Risk Factors Contributing to Cognitive Decline

Various biological systems work in conjunction to maintain optimal brain function and cognitive ability. Perturbations in the harmony of these systems, caused by such age-associated insults as chronic inflammation[40] oxidative stress,[41] insulin resistance,[42] declining hormone levels,[43] and endothelial dysfunction,[44] result in physical deterioration of the brain and subsequent cognitive decline.

Oxidative Stress

The brain is particularly susceptible to oxidative damage since it consumes roughly 20% of the oxygen used by the entire body, and because it contains high concentrations of phospholipids, which are especially prone to oxidative damage in the context of high metabolic rate.[45] As we age, there is a significant and progressive increase in the level of oxidatively damaged DNA and lipids in the brain; this is true even for healthy individuals.[46] Over time, this free radical damage leads to the death of neurons.

Numerous studies have implicated oxidative stress in the pathology of mild cognitive impairment and Alzheimer's disease alike.[47,48,49]

In a study of 338 individuals, researchers analyzed blood samples from patients with various neurodegenerative diseases and found that the antioxidant capacity of their blood was reduced by as much as 28%, relative to healthy controls. Subjects with a neurodegenerative condition also exhibited significantly increased levels of thiobarbituric acid reactive substances, a marker of free radical damage.[50]

A separate study, in which researchers examined the plasma of 34 subjects with mild cognitive impairment, 45 with Alzheimer's disease, and 28 age-matched healthy controls, revealed that patients with mild cognitive impairment or Alzheimer's disease displayed markedly increased oxidative damage. Subjects with mild cognitive impairment or Alzheimer's disease exhibited increased protein oxidation (protein carbonyls) and decreased levels of glutathione, a powerful endogenous antioxidant.[51]

In aged rodents exhibiting signs of cognitive deterioration, increased oxidation of key proteins involved in neuronal metabolism and energy production has been observed.[52] Old animals also display dramatically reduced ability to combat oxidative stress, as assessed by a loss of efficiency of thiol reducing systems.[53]

Inflammation

The inflammatory process in the brain is unique in that the blood-brain barrier (BBB) (tight layer of endothelial cells that separates the brain from regular systemic circulation), during healthy conditions, prevents the infiltration of inflammatory agents and allows only select nutrients and small molecules into the central nervous system (CNS).[54] However, chronic systemic

inflammation induced by stimuli such as cigarette smoking, obesity, disrupted sleep patterns and poor dietary habits compromises the integrity of the BBB, allowing irritants to enter the brain and stimulate the production of inflammatory cytokines, such as IL-1β, IL-6 and IL-18.[55] Inside the CNS, these cytokines impair *neurogenesis*, the process by which new neurons are generated.[56,57,58,59] Aside from inhibiting neurogenesis, some inflammatory cytokines, such as IL-1β, IL-6 and TNF-α damage and destroy existing neurons.[60,61]

Several studies have linked biomarkers of inflammation with cognitive impairment.

A prospective study of 779 healthy, high-functioning men and women found that subjects in the highest tertile (one-third) for blood levels of IL-6 were significantly more likely to score below the median when assessed for cognitive function at baseline. During follow-up seven years later those same individuals more frequently exhibited declines in cognition compared to their counterparts with lower baseline IL-6 levels.[62]

In a study of 97 women between 60 and 70 years of age, elevated baseline high sensitivity C-reactive protein (hs-CRP) levels were correlated with worsening of memory at 12 years follow-up. This data led the authors to conclude that "*hs-CRP may be a useful biomarker to identify individuals at an increased risk for cognitive decline*."[63] Likewise, in a study assessing over 4,000 subjects, higher levels of CRP *and* IL-6 were found to be associated with decreased cognition and executive function. IL-6 was also associated with steeper declines in memory performance during follow-up at up to five years.[64]

Another study found that, even in healthy individuals, baseline CRP levels were inversely correlated with the results of a learning and recall test at follow-up six years later. The investigators concluded that "*relatively high concentrations of… CRP may be indicative for impaired cognitive performance*." [65] In a similar study, biological markers were measured in the blood of 93 healthy individuals aged 57 years (mean). At six years follow-up time, those individuals with the highest baseline CRP levels scored lower on a Word Learning test. In this study it was concluded that "*concentrations of serum markers related to inflammation…are not only associated with Alzheimer's disease, but also with cognitive functioning in the cognitively healthy aging population*."[66]

The deleterious effects of inflammation on cognitive function are observable in real-time as well. Researchers administered a typhoid vaccination, which is known to induce an inflammatory response, or a placebo injection to 16 healthy men aged 18 to 35. Study subjects then completed a series of tests designed to assess cognitive vigilance. Participants who received the typhoid vaccination exhibited significantly slower reaction times than their counterparts who received the placebo, and the degree of delay in reaction time correlated with the intensity of inflammation, as measured by circulating IL-6 levels.[67]

Postoperative Cognitive Dysfunction

Acute confusion and impaired consciousness within a few days after major surgery is quite common, especially among older adults. This phenomenon is called *postoperative delirium*, and typically resolves before hospital discharge.[454] Whether or not general surgery under anesthesia directly causes long term cognitive problems—termed *postoperative cognitive dysfunction*—is less clear. While there may be a true effect in some people, current evidence suggests that surgery and anesthesia are not robustly and directly linked to long-term cognitive impairment in most patients.[455-457]

Ongoing research has not found strong evidence of a link between persistent cognitive deficits and major surgery independent of overall health of the patient and their cognitive status trajectory *before* the surgery.[457-459] Predisposing factors to worse cognitive outcomes after surgery include preexisting low-grade cognitive decline and early Alzheimer-type changes.[456,460] The observational evidence linking surgery to cognitive decline is relatively weak, and rigorous study data suggest any true effect on long-term cognitive function is negligible.[459,461] It may be that much of the apparent decline in cognitive function observed after surgery in older people is attributable to the *post hoc ergo propter hoc* fallacy— "after this, therefore because of this." But the expected continuation of a preexisting cognitive decline trajectory is thought to be the true culprit in many cases.[457]

One study found that, in pairs of middle-aged to elderly twins—who have very similar genetic and biochemical susceptibility —when one had undergone major surgery and the other had not, their cognitive scores were nearly identical. Another analysis in this study compared the twin who underwent surgery to a control group and found a small but clinically insignificant tendency to a lower cognitive score.[459] In a meta-analysis that pooled data from 19 studies, no clear association was found between general anesthesia and dementia risk. Nevertheless, when the analysis was limited to studies that used records of anesthesia rather than subjective patient recall, the authors found a small increased risk of dementia in those who had received general anesthesia, highlighting the need for high-quality study designs when this phenomenon is studied in the future.[461]

The current lack of evidence does not mean that post-operative cognitive dysfunction is not worthy of a clinician's attention. Some studies have indeed found that surgery and general anesthesia are associated with negative effects on cognition in the elderly,[462,463] negatively impacting the brain's immune system,[463] and that post-operative cognitive dysfunction that persists three months after surgery is associated with an increased risk of dying from any cause.[464] As surgical trauma induces a body-wide surge in inflammation, it has been proposed that inflammation of the brain, and failure to promptly resolve inflammation, may be causative factors for this syndrome. It has been proposed that measures to mitigate the

trauma and inflammation resulting from major surgery may help prevent this problem.[456,460]

Novel treatments for preventing post-operative cognitive dysfunction (POCD) are currently under investigation. Perhaps one of the best-studied ones is ulinastatin, an enzyme-inhibiting agent that can be either synthesized or isolated from human urine.[465] It is used in several Asian countries, but not yet approved in the United States.[466] A 2016 review of the scientific literature found five randomized controlled trials examining intravenously-administered ulinastatin's effect on POCD. In these trials, which enrolled a total of [461] elderly patients, ulinastatin reduced POCD compared to control treatment at three and seven days after surgery, but not on the day immediately following the procedure. Ulinastatin also reduced levels of the pro-inflammatory cytokine interleukin-6 within two days after surgery.[467] A 2017 controlled clinical trial confirmed these results. In this study, 80 elderly patients receiving chemotherapy and undergoing radical esophagectomy were randomized to ulinastatin or a control group. Those in the ulinastatin group experienced less POCD seven days after surgery, an effect the authors hypothesized might have resulted from the observed lower levels of interleukin-6 and C-reactive protein, and higher levels of the protective cytokine interleukin-10.[468]

Two natural interventions have attracted attention for the prevention of POCD. In a randomized controlled trial, 61 patients aged 30–70 years undergoing cardiopulmonary bypass received either 2 capsules of a *Valeriana officinalis* root extract per day or placebo. The intervention started a day before surgery and continued until 60 days after surgery. Subjects treated with the root extract had a significantly lower likelihood of POCD than those in the placebo group.[469] A second intervention trial, underway as of mid-2018, is evaluating the potential of N-acetylcysteine as a treatment for POCD.[470]

Many of the integrative interventions discussed in this protocol that may help promote brain health may also help promote healthy postoperative cognitive function. Also, refer to the Surgical Preparation protocol, which reviews many integrative interventions that may support surgical recovery in general.

Hormonal Imbalance

Distributed throughout the brain are steroid hormone receptors which function to regulate the transcription of a vast array of genes involved in cognition and behavior.[68] Adequate steroid hormone receptor activation in the brain is a fundamental determinant in many aspects of our lives that we take for granted. When hormonal imbalances or deficiencies disrupt receptor activation, cognitive deficits and emotional turmoil are the result.

Estrogen. Animal models indicate that experimentally-induced alterations in the levels of steroid hormones, particularly estradiol, in the brain cause significant behavioral changes observable within minutes, leading some researchers to conclude that steroid hormones actually have the capacity to function directly as neurotransmitters in the central nervous system.[69] In humans, suboptimal (low) levels of estradiol are associated with decreased scores on standardized assessments of cognition in both men and women.[70] Postmenopausal women with higher levels of endogenous estradiol also have better semantic memory than do those deficient in the estrogen.[71] Accordingly, postmenopausal women treated with estradiol displayed improvements in executive function compared to those taking a placebo.[72]

Testosterone. Maintaining optimal levels of testosterone can help preserve cognitive ability as well. In a study involving over 500 aging men and women, higher levels of testosterone were linked with better performance on the Mini-Mental State Examination at baseline. Men with the lowest levels of testosterone at the beginning of the study period were more likely to exhibit a sharp decline in cognitive ability over the following two-year period as well.[73] Several other studies also conclude that testosterone levels are positively associated with multiple aspects of cognitive function.[74,75]

Aging men given testosterone replacement therapy display improved cognitive function. In one study healthy men between the ages of 50 and 85 years responded to supplemental testosterone restoration treatment with significantly improved spatial and verbal memory, and spatial ability.[76] Likewise, men with mild cognitive impairment or Alzheimer's disease responded to testosterone therapy with enhanced spatial and verbal memory, and constructional abilities.[77]

Experimental studies indicate that the connection between testosterone and cognitive function is due in part to the dependence of the hippocampus on androgens to maintain synaptic density. Intriguing data shows that male non-human primates devoid of androgens have a dramatically reduced number of synapses in the hippocampus, which is of paramount importance for consolidation of short-term and long-term memory, as well as learning.[78] Additional experimental data shows that hippocampal synaptic maintenance is androgen dependent.[79]

Dehydroepiandrosterone (DHEA). Age-associated decline in levels of the adrenal hormone dehydroepiandrosterone (DHEA), which is very active in the central nervous system,[80] are also tied to worsening cognitive performance.[81] In a study involving over 750 aging subjects, Mini-Mental State Examination (MMSE) scores were significantly associated with levels of DHEA-s, the sulfated metabolic derivate of DHEA, which is more highly concentrated in humans. Moreover, those individuals with the lowest levels of DHEA-s at baseline displayed greater cognitive decline over time than those with higher initial levels.[82] In a separate community-based study involving nearly 300 healthy women, levels of DHEA-S correlated positively with superior executive function, concentration, and working memory.[83] Accordingly, in a double-blind, placebo controlled clinical trial, six-months of supplementation with 25 mg of DHEA daily improved measures of cognitive function, especially verbal fluency, in

aging women.[84]

Pregnenolone. Another neurosteroid, pregnenolone, is also involved with a number of cognition-related functions within the brain. For example, experimental studies indicate that pregnenolone modulates neurotransmitter signaling through interaction with select receptor sites, which translates to improvements in long-term memory in rodents.[85,86] In human clinical trials, supplementation with pregnenolone improved cognition in subjects with neurological disorders.[87] Additionally, levels of pregnenolone metabolites are reduced significantly in the prefrontal cortex, an area involved with higher-order processing, in Alzheimer's disease patients, leading some researchers to speculate that pregnenolone levels may be relevant in the pathology of the disease.[88]

Research indicates that DHEA, pregnenolone, and metabolites thereof exert numerous activities in the central nervous system through activation of the *Sigma-1 receptor.* This effect may confer benefits including protecting neurons against ischemia (i.e. stroke),[89] and enhancement of long-term potentiation (memory formation).[90]

Thyroid hormones. During the developmental period thyroid hormones play a critical role in ensuring proper growth and maturation of the brain.[91] Thyroid hormone levels may also be related to cognitive function in adults, though the evidence in this area is inconsistent. However, limited associations with both hypo- (low) and hyper- (high) thyroid function and cognitive impairment exist in the peer reviewed literature, thus maintaining levels of TSH, T3, and T4 within normal ranges is suggested.[92]

Cerebrovascular Health

The brain depends on the carotid arteries to obtain the oxygen and nutrient-rich blood that it needs to sustain its high rate of metabolic activity. The carotid arteries emerge from the aorta and carry blood through the neck into the brain where they branch and diverge into many smaller capillaries, which facilitate circulation across the various brain regions. Like other blood vessels, the carotid arteries and their subsidiaries (smaller branches) are susceptible to endothelial dysfunction, dysregulation and damage to the delicate cells that line our blood vessels. Endothelial dysfunction is a critical step in both the initiation, and progression, of atherosclerosis.

Figure 2: Illustration showing the cerebrovasculature (bottom view of human brain)

If the integrity of the blood vessels that supply the brain is compromised, cognition suffers as a result. Multiple correlates between measures of vascular health and cognitive function are identified in the peer-reviewed literature.

HDL levels. HDL serves to shuttle cholesterol from the blood vessel walls back to the liver for excretion, and thus insufficient levels of HDL are associated with increased endothelial dysfunction and arterial plaque deposition. Studies have linked low HDL levels with declining brain health and function.

Researchers examined the brains of 183 subjects, mean age 58 years, using magnetic resonance imaging (MRI). Tests revealed that HDL levels were positively associated with brain grey matter volume. Not surprisingly, then, subjects with higher HDL levels also scored significantly higher on a visuo-spatial memory test than their counterparts with lower HDL levels. These findings lead the investigators to conclude that "*adults with decreased levels of HDL cholesterol may be experiencing cognitive changes and grey matter reductions in regions associated with neurodegenerative disease and therefore, may be at greater risk for future cognitive decline.*"[93]

In a study of 139 very elderly subjects, plasma HDL levels were strongly associated with cognitive acuity. Subjects with higher HDL levels performed much better on the Mini-Mental State Examination (MMSE) than those with lower HDL levels. In fact, "*each decrease in plasma HDL tertile (74.9 +/- 2.1, 50.6 +/- 0.5, and 36.8 +/- 1.0 mg/dl) was associated with a significant decrease in MMSE [score].*"[94]

Homocysteine. Homocysteine is an endogenous amino acid derivative which damages the endothelial cells that line the inside of blood vessels and contributes to the pathogenesis of atherosclerosis and vascular dysfunction.[95] Elevated homocysteine has been linked with reduced blood flow to the brain,[96] memory impairment,[97] poorer global cognitive function,[98] smaller overall brain volume,[99] and increased silent brain infarcts (subclinical stroke-like blood vessel occlusions in the brain).[100]

In a randomized, placebo-controlled clinical trial, which included over 5,500 subjects with known cardiovascular disease, treatment with the homocysteine-lowering B vitamins folic acid (2.5 mg), B6 (50 mg) and B12 (1,000 mcg) was shown to significantly reduce the risk of stroke versus placebo, highlighting the link between cerebrovascular health and homocysteine levels.[101]

Similarly, lowering homocysteine in individuals over 70 years of age through supplementation with 800 mcg folic acid, 500 mcg B12, and 20 mg B6 daily for a period of 24 months was shown to reduce the rate of brain atrophy by 53% versus placebo control in a randomized, double-blind trial. Subjects receiving the homocysteine lowering B-vitamins also scored much better on their final cognitive tests at the end of the study period.[102]

Hypertension. Small, delicate capillaries, like those that perpetuate the flow of blood throughout the brain, are particularly

susceptible to damage caused by elevated blood pressure. Chronic hypertension leads to the breakdown of cerebrocapillaries, a condition associated with the development neurodegenerative diseases and cognitive impairment.[103]

A case-control study of over 700 patients found a statistically significant correlation between blood pressure and rate of cognitive decline over a six-month period for subjects younger than 65 years.[104] Accordingly, an observational study of more than 1,800 people revealed that individuals taking an antihypertensive medication were less likely to have dementia at the study onset, and were also less likely to develop dementia over the following three year period. Significantly, subjects who *did* have dementia at baseline and were *not* taking blood pressure medication exhibited a two-fold faster rate of cognitive decline than demented individuals with medication-controlled hypertension.[105]

In a study which followed 717 individuals for 38 years starting from age 45, researchers found that subjects with systolic blood pressure ≥140 mmHg throughout the study period "*performed consistently less well than the normal systolic blood pressure subgroups on a composite measure of verbal learning and memory*."[106]

Evidence suggests that blood pressure of 115/75 mmHg significantly reduces the risk for cardiovascular disease,[107] and thus may be an ideal target for those who wish to maintain optimal cognitive performance as well.

Diabetes and Insulin Resistance

Due to the high metabolic demand for energy in the brain, even small perturbations in glucose metabolism can noticeably impact cognitive performance. Diabetes (hyperglycemia) has been linked with lower levels of neuronal growth factors,[108] decreased brain volume,[109] and higher incidence of all types of dementia.[110]

Cerebral glucose metabolism was measured by fludeoxyglucose – positron emission tomography (FDG-PET) in 23 adults aged 74 years (mean), who met criteria for diabetes or pre-diabetes. The results were compared to those of six 74 year old (mean) adults without diabetes or pre-diabetes. Subjects were asked to memorize and recall a list of 20 random words they heard through a pair of headphones. FDG-PET scans revealed markedly different patterns of glucose utilization and brain activity between diabetic / pre-diabetic subjects and healthy controls during the memorization task. Subjects with healthy glucose metabolism remembered more words upon recall attempt. Interestingly, FDG-PET scans of those with pre-diabetes / diabetes resembled brain scans of Alzheimer's patients.[111]

Researchers in another study compared MRI-assessed manifestations of cerebral degeneration in 89 non-demented subjects with type-2 diabetes to 438 age-matched healthy controls over a three-year period. Individuals with diabetes displayed increased progression of brain atrophy, and performed less well on tests of cognitive performance and learning. The investigators concluded that "*our data showthat elderly patients with [type-2 diabetes] without dementia have accelerated progression of brain atrophy with significant consequences in cognition compared to subjects without [type-2 diabetes]. Our findings add further evidence to the hypothesis that diabetes exerts deleterious effects on neuronal integrity*."[112]

In over 1,300 aging men, researchers observed an inverse correlation between fasting insulin levels and cognitive function in non-diabetics. Baseline insulin levels were assessed and followed by a battery of cognitive testing an average 3.3 years later. Subjects with higher initial insulin levels scored more poorly on all four tests administered. These results indicate that "*higher fasting insulin and greater insulin secretion in older men may be related to overall cognitive decline, even in the absence of diabetes*."[113]

Obesity

Adipose tissue secretes molecules that directly influence multiple functions within the brain.[114] There is a clearly established reciprocal relationship between adiposity (amount of body fat) and overall brain volume and cognitive function. In other words, as bodyweight increases, brain volume drops and cognitive function worsens.[115,116,117,118]

In a study utilizing MRI brain imaging technology to explore the link between obesity and brain volume, researchers discovered that visceral abdominal obesity in particular was associated with deteriorating brain structure. This was true even in individuals without pre-existing cognitive deficits. The findings were statistically significant and independent of vascular risk factors and overall BMI. [119]

Similar findings were reported by another group, but this time in 700 patients with a prior diagnosis of Alzheimer's disease or cognitive impairment. Investigators identified a strong correlation between higher BMI and brain volume deficits in the frontal, temporal, parietal, and occipital lobes. It was concluded that "*cardiovascular risk factors, especially obesity, should be considered as influencing brain structure in those already afflicted by cognitive impairment and dementia*."[120]

In 90 healthy middle-aged and older adults (ages 54 – 81), who performed tests of manual dexterity, motor speed, and executive function, greater central obesity as manifested by higher waist circumference was associated with poorer performance. Not surprisingly, high blood pressure exacerbated the correlation between increasing waist circumference and declining cognition; "*in healthy older adults, there are similar, negative relations of central and total obesity to cognitive function that are potentiated by higher [blood pressure] levels*."[121]

Mid-life obesity was strongly linked to later-life dementia in over 1,000 participants in a longitudinal study carried out over a 36

year period. Subjects with the greatest waist diameters at baseline were nearly three-fold more likely to develop dementia over the following three decades. The investigators in this study concluded that "*central obesity in midlife increases risk of dementia independent of diabetes and cardiovascular comorbidities.*"[122]

Psychological Risk Factors Contributing to Cognitive Decline

There is a tendency to focus on the biological aspects of a disease state because they are perceived as tangible, measurable, and modifiable. However, more loosely defined facets of our lives related to our psychological condition contribute to our mental fluency as well. The ways in which the brain is utilized and stimulated impact its functional state at all ages.

Psychoanalytical tests have found that cognitive impairment is closely correlated with traits such as boredom-proneness, loneliness,[123] small social network,[124] and high stress.[125]

Anxiety and Stress

Research in patients with anxiety has shown that, compared to non-anxious control subjects, those with high-anxiety levels must exert greater effort (dedicate more brain resources) to maintain the same level of performance on cognitive tests.[126] More severe anxiety is also predicative of earlier conversion from mild cognitive impairment to Alzheimer's disease.[127] In men, even subclinical (low-level) anxiety is tied to cognitive impairment.[128]

Excessive stress leads to cognitive dysfunction as well. In a study involving 36 women between the ages of 25 and 53, those with the highest work-related stress levels displayed decreased attention and visuo-spatial memory.[129] Likewise, in a cohort of 811 aging men, subjects reporting higher stress levels scored lower on the Mini-Mental State Examination than their low-stress counterparts. This indicates that "*psychological stress had an independent inverse association with cognition…*"[130]

Posttraumatic stress disorder (PTSD) is a condition characterized by chronic, lingering anxiety and stress related to a traumatic event in the past. A comprehensive review of eight studies highlighted a strong association between PTSD and smaller brain size (total brain volume).[131] The duration of PTSD influences the extent to which the brain deteriorates; developing effective coping strategies as soon as possible may help to limit PTSD-induced decreases in brain volume.[132]

Meditation is an effective method for relieving stress. With the connection between stress and cognitive dysfunction in mind, researchers studied the effects of an 8-week audio-guided meditation program on cerebral blood flow and cognition in 14 subjects with memory problems. Tests revealed that meditation significantly increased cerebral blood flow in several major brain regions. Improvements in tests of verbal fluency and logical memory were attributed to meditation as well.[133]

Depression

An intimate relationship exists between depression and cognitive dysfunction. Many studies have closely examined this link and allude to the intertwinement of these two conditions, rather than a causal effect of one on the other. Interestingly, depression seems to worsen cognitive dysfunction, but poorer cognitive health predisposes aging individuals to depression as well.[134]

In fact, studies designed specifically to assess age-related cognitive performance in depression show an interrelationship between the two conditions. A group of aging subjects diagnosed with depression completed various cognitive tests and their results were compared to those of age and sex – matched, non-depressed control subjects. More than half of the depressed subjects scored below the 10th percentile of the control group on the battery of tests they completed. The conclusion drawn from this evidence was that "*late-life depression is characterized by slowed information processing, which affects all realms of cognition.*"[135]

Continuing research has lead to the delineation of "*depression-associated reversible dementia,*" which is cognitive impairment associated with depression that subsides upon improvement of depression. Nonetheless, in a study of 57 elderly subjects with major depression, those who displayed depression-associated reversible dementia were nearly **five times more** likely to develop true dementia over a roughly three-year period.[136]

Several cognitive and neuropsychological deficits accompany depression, including impairments in executive function, attention, episodic memory, visuo-spatial skills and information processing.[137] Other research indicates that deterioration in structural integrity of specific brain regions involved in emotional processing is observed in depressed patients.[138]

Social Network and Personal Relationships

Several studies have suggested that maintaining a large network of friends and other personal relationships, and regularly engaging in social and productive activities is associated with a decreased risk of cognitive decline.[139,140] Conversely, social *disengagement*, defined as having very few or no social relationships, is a strong risk factor for cognitive decline.[141]

Among 2,249 women aged 78 or older, those with smaller social networks at baseline had a significantly greater chance of having developed dementia within one year than women with larger social networks. The investigators stated that "*our findings suggest that larger social networks have a protective influence on cognitive function among elderly women.*"[142] In another study, researchers assessed work history data for nearly 1,000 subjects, who were then followed for up to six years. Participants

in the study whose careers involved regularly working closely with people on complex tasks were much less likely to develop dementia over time than subjects who did not regularly work closely with other people.[143]

Sixteen behavioral measures were correlated with Mini-Mental State Examination (MMSE) scores for 1,437 elderly subjects in an Austrian study. Among other measures, living alone and perceiving life as being generally stressful were independently associated with lower MMSE scores.[144] These findings are supported by a separate study that identified being unmarried as an independent risk factor for cognitive impairment in over 7,000 Italian subjects.[145]

Social integration, defined by marital status, volunteer activity, and frequency of contact with children, parents, and neighbors, conveys a memory preserving effect in elderly adults. Over a six-year period, memory among those with the lowest level of social integration declined at twice the rate of subjects with the higher levels of social integration.[146]

Maintaining close ties with friends and loved ones, and being involved in various group-oriented activities, especially outdoors, is an effective method for stimulating and maintaining your brain as you age.

Mental and Physical Activity

The brain consists of a vast network of approximately 90 billion (10^9) neurons interconnected by 1,000 trillion (10^{15}) synaptic junctions.[147] Each mental and physical task that we perform stimulates this massive network in a unique way. Regular stimulation of diverse synaptic pathways by engaging in a wide range of mentally and physically challenging activities directly influences our ability to learn by enhancing synaptic plasticity, and initiating the process of neurogenesis in critical areas of the brain.[148,149] In fact, it is now clear that neural plasticity allows the structure and function of the adult human brain to change significantly as a result of new experiences.[150]

Physical Activity and Brain-Derived Neurotrophic Factor

A critical driving force behind neural plasticity (and therefore overall cognitive function) is a protein called brain-derived neurotrophic factor, or BDNF. BDNF acts upon areas of the brain involved in learning, memory, and higher-order thinking to stimulate genesis of new neurons, survival of existing neurons, and synaptic adaptation.[151,152,153] Low levels of BDNF are observed in a variety of brain disorders, including cognitive decline, depression, dementia, and Alzheimer's disease.[154,155]

Physical exercise is known to enhance cognitive function in humans and other animals, and many researchers now believe that an increase in levels of BDNF induced by exercise mediates this improvement.[156,157,158] Several studies have demonstrated that moderate to high intensity aerobic or anaerobic exercise induces sharp (intensity-dependent) increases in BDNF levels in humans.[159,160]

Gold *et al* noted a marked increase in serum BDNF levels induced by a 30-minute bout of moderate intensity cycling; this was observed in both healthy subjects and in patients with multiple sclerosis.[161] These findings are supported by Tang *et al* who found that only 15 minutes of a high-intensity stair climbing exercise significantly bolstered serum BDNF levels in healthy men.[162] At the highest intensity level, exercise induces sharp increases in serum BDNF levels in as little as three minutes, as reported by Winter *et al*, who documented the effects of very-high intensity sprinting exercises in healthy young men.163 In this last study, the post-exercise spike in BDNF levels corresponded with a 20 percent improvement in short-term memory.[164]

Animal models allow scientists to more closely study the dynamic effect of physical activity on the brain. Work conducted by researchers in Taiwan indicates that, while both leisurely (voluntary) physical activity (ie. briskly walking in the park) and targeted physical exercise (ie. going to the gym) boost levels of BDNF and enhance plasticity in animals, they do so in different regions of the brain.[165] These findings highlight the importance of not only engaging in exercise routines, but leading a generally active lifestyle as well in order to promote overall brain health.

The beneficial effects of exercise on brain health appear to be limited only by the duration of exercise. Studies conducted in rats reveal a direct correlation between the amount of time spent exercising (wheel running) and the genetic expression of BDNF. In other words, the longer the rats exercised, the more robust the increase in BDNF gene expression.[166]

The protective effects of regular exercise on cognitive health were documented in a recent comprehensive analysis of 15 studies including over 33,000 subjects who were followed for up to 12 years. Individuals with the highest levels of physical activity were a striking 38% less likely to show signs of cognitive decline over time compared to those with very-low activity levels. Amazingly, even low to moderate levels of physical activity conveyed a robust 35% reduction in risk for cognitive decline. The importance of physical activity for brain health was reflected in the authors' concluding statements: "*the present results suggest a significant and consistent protection for all levels of physical activity against the occurrence of cognitive decline.*"[167]

Mental Activity, Brain Plasticity, and Cognitive Reserve

Neural plasticity, the dynamic ability of the brain to adapt and respond to novel stimuli in a unique and reinforceable way, is a pivotal aspect of cognition. Plasticity serves as a key medium for the effects of practicing a physical activity – i.e. getting better at a physical task over time. As we practice an activity repetitively signals are transmitted through the brain in a specific pattern over and over again. This redundant signaling ultimately strengthens the connections between neurons in the signaling pathway required to execute the task, leading to greater efficiency and accuracy of

signal transmission.

An important limitation of *physical* practice, though, is that improvements in ability are generally confined to the task being practiced. In other words, practicing tennis does not increase proficiency in bowling. Repetitive *mental* stimulation, on the other hand, exerts domain-wide improvements that impact other tasks as well. To elaborate, practicing a mentally challenging activity that requires utilization of higher-order cognitive processes, playing chess for example, can improve fluency in other activities that require similar cognitive processes, like driving a vehicle.[168,169]

Brain plasticity also serves as a prerequisite for a more global effect known as cognitive reserve. This phenomenon arises from, and is dependent on, synaptogenesis – the formation of new synapses, the hallmark physical affect of mental training.

The introduction of novel cognitive stimuli encourages the brain to establish new neural networks through synaptogenesis, which can then be used to bypass breakdowns in other neural networks arising from age-related or pathological deterioration in brain circuitry.

Cognitive reserve is measurable as a function of life experiences and studies have shown that cognitive reserve scores correlate with overall cognitive function in an aging population.[170] In subjects with Alzheimer's disease or mild cognitive impairment, higher cognitive reserve mitigates the loss of function typical with these conditions.[171] This same study found that individuals with higher cognitive reserve scores performed better on assessments of visuo-spatial ability than those with lower scores, despite presenting with equal pathologic progression of Alzheimer's disease or mild cognitive impairment as assessed by brain imaging.

Just as the desire to maintain a fit and functional body into late life necessitates regular physical exercise, ensuring cognitive dexterity with advancing age requires constantly pushing the brain to new limits in order to evoke plastic changes that strengthen existing, and encourage new, synaptic connections. This becomes clear when considering that individuals with mentally demanding careers appear to be at significantly decreased risk of developing Alzheimer's dementia in later life, compared to those whose careers centered on physical labor.[172]

Plasticity is an intrinsic property of the brain maintained throughout life; and so cognitive stimulation and training enhance cognitive reserve and convey protection against loss of brain function regardless of age.[173] In a study including nearly 500 individuals with clinical cognitive impairment, computerized cognitive training significantly improved several measures of cognitive function.[174] Improvement was still evident up to three months post training in some cognitive assessments. Moreover, as little as two hours of cognitive training initiates structural changes in the brain suggesting that those who chose to challenge their intellectual capacity reap the benefits instantaneously.[175]

A 2005 case study of a chess player reveals the true compensatory ability of the brain given regular cognitive stimulation. The chess player, an aging gentleman whom heretofore displayed excellent cognitive function, presented with complaints of slight memory loss, which over the next two years progressed into mild cognitive impairment. The man then fell ill with an unrelated illness and passed seven months later. The autopsy revealed that he had been living with advanced Alzheimer's pathology in his brain, which would normally cause severe deterioration of cognitive ability. Remarkably, the man displayed only mild cognitive impairment until his death.[176] Regularly playing chess had imbued the gentleman with a great deal of cognitive reserve, allowing for relatively normal neural efficiency despite stark deterioration of the structural integrity of the brain.

Speaking more than one language is also a strong inducer of plasticity and cognitive reserve. Learning a second language requires the brain to constantly categorize information in ways that are unnecessary when only a single language is spoken; this establishes numerous new neuronal communication streams. In a study of more than 200 individuals clinically likely to have Alzheimer's disease, being bilingual was found to delay that onset of symptoms by over five years, and delay diagnosis by nearly four and a half years relative to monolingual speakers.[177]

Cognitive stimulation and training also benefit the brain by enhancing cerebral blood flow. Mozolic *et al* have shown that an eight-week attention and distractibility cognitive training program significantly increased blood flow to the prefrontal cortex, a brain region involved in personality expression and decision making. The control group in this study, who were exposed to education material, but not intensive cognitive training, displayed no increase in cerebral perfusion.[178]

A lifestyle incorporating frequent physical exercise, continual learning, and regular cognitive stimulation is likely to be the most effective means for preserving, and possibly enhancing, cognitive function at any age.

Medical Approaches to Combating Cognitive Decline

While various pharmacologic therapeutics have been studied in hopes of identifying an effective intervention for preserving cognition with aging, and preventing diseases of the brain such as Alzheimer's disease, evidence in support of medical therapies are equivocal at best.[179] However, preliminary data suggests that some drugs may provide limited benefits for brain health, and thus may adjunctively synergize with increased mental and physical activity levels, dietary changes, and neutraceutical options to optimize brain function with advancing age.

Piracetam

Piracetam has been studied in a wide-range of patient populations, and has demonstrated small benefits in a variety of models of neurological disorders. Multiple mechanisms for the observable effects of piracetam on brain function have been proposed, though a precise description of its mechanism(s) of action has yet to be elucidated. Preliminary studies suggest that piracetam may modulate the signaling of multiple neurotransmitter receptors,[180] and improve neuronal membrane fluidity.[181]

A recent comprehensive review which assessed the efficacy of piracetam in older subjects suggests that the drug may provide appreciable benefits for cognitive dysfunction. The reviewers concluded that *"…the results of this analysis provide compelling evidence for the global efficacy of piracetam in a diverse group of older subjects with cognitive impairment."*[182]

Zileuton

5-lipoxygenase (5-LO) is an enzyme that produces several pro-inflammatory lipid molecules, most of which are known as leukotrienes.[471,472] 5-LO and some of the leukotrienes it produces have been implicated in the inflammation that accompanies various chronic diseases, including Alzheimer's disease.[473-475] These inflammatory mediators have also been implicated in other tauopathies, which are neurodegenerative conditions in which toxic protein deposits, known as tau protein, accumulate inside neurons. Alzheimer's disease is a type of tauopathy.[476,477]

A 2018 study suggests zileuton (Zyflo), a leukotriene inhibitor approved over two decades ago to treat asthma, may have the potential to reduce neurodegeneration associated with tau protein accumulation.[478,479] Using an animal model of neurodegeneration, the study tested whether inhibiting leukotriene synthesis could help after cellular damage in the nervous system has already started. Twelve-month-old mice with a tauopathy were randomized to receive zileuton or placebo for 16 weeks. As expected, at the beginning of the study memory and spatial learning were impaired in the mice with the tauopathy compared with control mice. Zileuton reduced these behavioral impairments. When the brains of the animals were examined, mice that received zileuton had about 90% fewer leukotrienes in their brains and about 50% less tau protein. The animals treated with zileuton also had decreased neuroinflammation and increased levels of three biochemical markers that reflect synaptic integrity.[480]

Other studies also report benefits with zileuton treatment in neurodegenerative diseases. In a mouse model of Alzheimer's disease, three months of zileuton treatment significantly decreased amyloid-beta levels between the neurons and improved cognitive function.[481] Another study on the same mouse model of Alzheimer's disease showed that zileuton treatment led to a significant improvement in working memory and communication among brain cells.[482] Similar findings have been reported in other preclinical studies as well.[483,484] Moreover, in rodent models of stroke, zileuton decreased inflammation, protected against brain damage, and improved neurological deficits.[485,486] Zileuton also inhibited 5-LO activation and cell injury in a laboratory model of Parkinson's disease.[487] In a laboratory study, zileuton protected mouse neurons against chemical toxicity caused by exposure to glutamate.[488]

Hydergine

Like piracetam, hydergine has been proposed to affect the brain in multiple ways. The drug, which largely fell out of clinical use decades ago after it was shown to be largely ineffective for Alzheimer's disease, is still incorporated by some integrative physicians into regimens for brain support. Proposed mechanisms include enhancing brain glucose utilization,[183] increasing acetylcholine signaling,[184] and preserving hippocampal structure with advancing age,[185] among others.

Collectively, data indicates that hydergine may be slightly more effective than placebo for treating dementia; however, a review concluded that *"the efficacy of Hydergine remains inadequately defined."*[186]

Deprenyl

Deprenyl, in low doses, is a selective MAO-B inhibitor, and thus slows the breakdown of various neurotransmitters in the central nervous system, especially dopamine, so it may enhance mood and energy.[187] The drug has been shown to preserve some regions of the rodent brain with increasing age,[188] and to ameliorate HIV-related cognitive impairment in a double-blind, placebo-controlled human trial.[189]

Centrophenoxine

Centrophenoxine is structurally related to dimethylethanolamine (DMAE), a metabolic precursor to acetylcholine. It has been shown that centropehnoxie increases acetylcholinergic synaptic signaling,[190] and improves memory and mental alertness in healthy elderly subjects.[191] Other proposed mechanisms by which centrophenoxine may benefit brain function are improving neuronal hydration through enhanced membrane fluidity,[192] and the ability to reduce neuronal oxidative stress.[193]

Dietary Considerations for a Healthy Brain

The exceptionally high rate of metabolism in the brain makes it particularly responsive to the nutritional content of the diet. A Western dietary pattern, typified by excess consumption of simple carbohydrates and dietary fat (in particular saturated fat and omega-6 polyunsaturated fatty acids), is a detrimental, yet alterable, modulator of cognitive function. Numerous studies have identified high intakes of simple sugars and saturated fats as being especially deleterious for brain health.[194,195,196] Transitioning to a slightly calorie-restricted Mediterranean diet high in mono- and poly- unsaturated omega-3 fats, fiber, and

polyphenols will provide the brain with nutrition to function at high capacity and efficiency.

Some dietary considerations that may be easily overlooked provide substantial brain benefits as well.

Calorie Restriction

Calorie restriction is the restriction of caloric intake to a level modestly below normal, typically 20% to 30% less, but the diet should be dense with micronutrients to maintain optimal nutrition. Caloric restriction is well-known for its ability to induce favorable changes in peripheral insulin sensitivity, which enhances insulin signaling in the central nervous system. The brain relies heavily on proper insulin signaling for a variety of functions that impact cognition, and so it is not surprising that caloric restriction has been shown to benefit cognitive function in many animal and human studies.[197,198]

A study conducted in 124 hypertensive individuals who led generally sedentary lifestyles found that four months of caloric restriction in conjunction with a diet designed to help control blood pressure produced several neurocognitive improvements in domains including executive learning and psychomotor speed.[199]

Caloric restriction also boosts levels of several neurotrophic factors, including BDNF, and thus creates an ideal environment for plastic adaptation of the brain in response to mental stimulation.[200]

Mediterranean Diet

A great deal of scientific literature validates the Mediterranean diet as a staple for those concerned with cardiovascular health, cognitive health, and longevity. The diet centers on "good" fats – mono- and poly-unsaturated fats, especially omega-3's and olive oil, multi-colored fruits and vegetables, and moderate red wine consumption.[201,202] Adherence to the Mediterranean diet has been linked with improved insulin sensitivity,[203] lipid metabolism[204], blood pressure,[205] reduced risk of developing cancer[206] or metabolic syndrome,[207] as well as an overall decrease in mortality.[208, 209]

The brain also benefits greatly from the health-promoting lipids and antioxidants that are ample in the Mediterranean diet.[210] An abundance of scientific literature concedes that adherence to the Mediterranean diet is associated with better cognitive performance in a variety of populations.[211]

In 1,393 individuals participating in a prospective study with follow up of 4.5 years, greater Mediterranean diet adherence was shown to decrease the risk of developing mild cognitive impairment by 28% compared to lesser adherence. Additionally, in those who consistently consumed a Mediterranean diet, but *did* develop mild cognitive impairment, risk of converting to Alzheimer's disease was cut by 48% relative to subjects whose diet deviated from the Mediterranean style.[212] Several additional studies have concluded similarly.[213,214,215]

Moderate Alcohol Consumption

While there is no question that heavy alcohol consumption is deleterious to nearly all aspects of health, including cognition, moderate alcohol consumption, characterized as two drinks daily, seems to convey protection against cognitive decline with aging. Fifteen studies were summarized in a recent comprehensive review which included data for over 36,000 subjects; those classified as "moderate" drinkers were roughly 25 – 30% less likely to develop Alzheimer's disease, vascular dementia, or any-type dementia, than non drinkers or heavy drinkers.[216]

Light to moderate alcohol consumption during midlife appears to convey protection against cognitive decline in late life. A study following over 1,400 individuals for nearly 23 years found that mid-life moderate drinkers were less likely to display signs of cognitive impairment later in life than their teetotaling and heavy drinking peers.[217]

Evidence suggests that red wine may be the alcoholic beverage of choice for maintaining cognitive health, as it contains many phenolic antioxidant compounds that are suspected to impede the pathological progress of Alzheimer's disease,[218] and limit the neurological consequences of high cholesterol.[219] Indeed, a seven-year longitudinal study including over 5,000 healthy subjects found that those who regularly drank a moderate amount of red wine scored better on every test of cognitive performance that the investigators administered than non-drinkers.[220] Other studies have produced similar findings.[221]

Many of the benefits of moderate drinking are likely attributable to alcohol's profound positive impact on levels of HDL ("good") cholesterol and enhancement of cholesterol efflux.[222,223,224] Alcohol consumption protects against cardiovascular and neurological disease and degeneration via mechanisms that may be thought of as hormetic (stress adaptive) in nature; the concluding statements of a recent review on this topic suggest that "*to a certain extent, moderate alcohol exposure appears to trigger analogous mild stress-associated, anti-inflammatory mechanisms in the heart, vasculature, and brain that tend to promote cellular survival pathways.*"[225]

Moderate Caffeinated Coffee Consumption

Coffee, like red wine, is an excellent source of antioxidant and neuroprotective compounds.[226,227,228,229] However, it has been suggested recently that the antioxidant compounds in coffee may synergize with caffeine to enhance the protective effect against brain pathology, and that decaffeinated coffee does not provide the same level of neuroprotection observed with caffeinated coffee.[230] Accordingly, a study which followed nearly 700 elderly men for a 10-year period revealed that coffee consumption, roughly equivalent to three cups daily, was associated with a 4.3 fold slower rate of cognitive decline when compared to those

subjects who did not drink coffee.[231]

A team of Scottish researchers recently found that coffee consumption was tied to superior reading ability and higher scores on some other cognitive assessments in a cohort of over 900 healthy adults.[232]

Moreover, a level of evidence that is strongly suggestive has accumulated indicating that caffeine itself exerts a variety of protective and augmentative effects in various cognitive domains.[233,234,235,236] Animal models have identified several mechanisms by which caffeine protects the aging brain, including preservation of blood-brain barrier integrity and suppression of brain and plasma amyloid-beta levels.[237,238,239]

In addition to preserving cognition, coffee consumption may also protect against type 2 diabetes and some cancers.[240,241] Black coffee or espresso appear to be superior choices when selecting a coffee beverage for health benefits, since adding sugar or non-dairy creamer has been shown to blunt the ability of coffee to increase the levels of antioxidants in circulation.[242]

Nutraceuticals to Support Brain Health

Healthy dietary habits ensure that food is an excellent source of nutrients that serve to support the brain both structurally and functionally. However, optimal neruoprotection and cognitive preservation often require micronutrient intakes in excess of those obtainable in a typical Western diet, or intake of specialized nutrients not common in most foods.

Many nutrients known to modulate physiological process important for brain health have been shown to slow cognitive deterioration, or enhance mental performance.

Fish Oil

Phospholipids are an integral component of all cells in the body, without which the integrity of cell membranes would fail, as would cellular function. In the brain omega-3 fatty acids are incorporated liberally into cellular phospholipid bilayers; DHA alone accounts for 40% of the phospholipid content of neuronal membranes.[243] Along with EPA, DHA plays a central role in neurotransmitter signaling and synthesis, and together the omega-3 fatty acids modulate numerous aspects of cognition and behavior.[244,245,246]

Evidence suggests that the typical Western diet is severely deficient in beneficial omega-3's, and supplies omega-6's in excess, which creates a fatty acid milieu that promotes inflammation and contributes to several age related degenerative diseases.[247] Numerous studies have concluded accordingly, indicating that supplementation with omega-3 fatty acids optimizes cognitive health.

Slightly less than two grams of fish oil daily, over a 24-week period, was shown to significantly improve scores on a standardized assessment of cognitive function in subjects with mild cognitive impairment. Increases in red blood cell EPA confirmed that supplemental fish oil was biologically available and responsible for the improvement in cognition.[248] A similar, but longer-term, study involving nearly 1,500 subjects found that daily omega-3 supplementation was independently associated with a dramatic reduction in cognitive decline over a 1.5 year period in an aging study population, compared to those not taking omega-3 supplements. Importantly, this study also found that dietary fish consumption was *not* associated with cognition, while omega-3 supplements were, highlighting the superiority of supplementing with omega-3's for supporting brain health.[249]

In addition to the numerous studies that have associated increased dietary omega-3 intake with better cognitive performance,[250,251] a more detailed study confirms the principle role the role of DHA in mediating this improvement. Researchers assessed serum phospholipid levels in 280 middle-aged (35 – 54) healthy study volunteers, which were then correlated to cognitive function. It was found that subjects with the highest serum levels of DHA performed significantly better in multiple domains of cognition than their cohorts with lower DHA levels. This association remained significant even after adjustment for various other confounding factors.[252]

Another way in which DHA may exert benefits is by working synergistically with other protective compounds, such as carotenoids.[505] An 18-month clinical trial investigated the effect of combined treatment with carotenoids and fish oil in 25 participants with Alzheimer's disease: 12 participants received a xanthophyll carotenoid supplement that provided 10 mg of lutein, 10 mg of meso-zeaxanthin, and 2 mg of zeaxanthin per day; 13 participants received the same carotenoid supplement plus 1 gram of fish oil, providing 430 mg of DHA and 90 mg of EPA daily. Those receiving the combination of carotenoids plus fish oil experienced greater increases in blood carotenoid levels and less progression of Alzheimer's disease compared with those receiving carotenoids alone, with reported improvements in memory, sight, and mood.

Wild Green Oat Extract

By age 45, the brain's levels of **dopamine** begin to diminish.[352] This not only makes people feel older, but is also involved in accelerated **brain aging**.

Dopamine depletion is largely caused by rising levels of the **MAO-B** enzyme. The ensuing dopamine deficiency strikes the brain's signaling system. The tragic result is cognitive decline, destruction of brain cells, reduction of youthful vigor/sexual desire, progression toward Parkinson's/neurological disorders, and a decreased lifespan.[353-358]

In a search for a safe method to block the insidious MAO-B enzyme, scientists have identified a bioactive extract of ***wild green oat*** that not only inhibits MAO-B and the resulting breakdown of dopamine, but ***enhances*** dopaminergic neurotransmission that normally declines with aging. These protective actions enable more dopamine availability for use by brain cells.

In human studies, the effects of ***wild green oat extract*** resulted in increased focus and concentration, processing speed, executive function, and working memory as well as other parameters of enhanced dopaminergic transmission.[359,360]

The discovery of the specific actions of ***wild green oat extract*** represents a significant advance in the technology of age management. It provides a method for halting some of the most destructive aspects of neurological aging, thus helping improve cognitive function and enhancing the quality of life.[361] Moreover, preclinical studies have shown that the well-known anti-aging drug deprenyl can extend the lifespan of some animals.[358,362-365]

Polyphenols and Anthocyanins

The disproportionately large metabolic demand of the brain compared to other parts of the body gives rise to an environment in the CNS primed for generation of cell-damaging oxygen free radicals. Polyphenolic antioxidants, such as resveratrol from grapes, catechins from green tea, and anthocyanins from blueberries are among the strongest naturally occurring free radical neutralizers, and several laboratory *in vitro* studies have confirmed the neuroprotective properties of these antioxidants. In the past, some scientists questioned the utility of these compounds in protecting neural health *in vivo* due to concerns over oral bioavailability. However, data clearly indicates that these protective compounds are not only adequately bioavailable ingested orally, but accumulate in the brain after oral ingestion, indicating blood-brain barrier permeability as well.[253,254,255,256,257]

Blueberries. Multiple animal studies have provided mechanistic insights into the well-documented brain health benefits of blueberry constituents. In addition to strongly attenuating neural oxidative stress, blueberry components also inhibit *acetylcholineesterase* (AChE), an enzyme responsible for catabolizing the important neurotransmitter acetylcholine, thus preserving acetylcholine-related memory and learning.[258] Blueberry supplementation also stimulates neurogenesis and enhances neuronal plasticity (adaptability) in the hippocampus, the region of the brain chiefly affected by Alzheimer's disease.[259] Other research has revealed that blueberry compounds may optimize cognitive performance through modulation of genetic expression within the brain.[260]

These biochemical actions translate into observable improvements in learning, memory, and overall cognitive performance resultant from blueberry supplementation or dietary fortification in both animal and human studies.[261,262,263]

Other beneficial effects of blueberry consumption include enhanced insulin sensitivity in obese subjects,[264] and improved vascular smooth muscle contractility after prolonged supplementation.[265]

Tea Polyphenols. Interest in studying components of tea in the context of brain health was generated by publication of epidemiological evidence which linked increased tea consumption with superior cognitive function in aged populations.[266,267] Investigations were fruitful in that they led to the elucidation of powerful tea constituents, including *epigallocatechin-3-gallate* (EGCG), and other phenolic antioxidants, and findings that these compounds possess tremendous disease modifying potential in Alzheimer's disease and the ability to preserve cognition in healthy aging individuals, and animals.[268,269,270]

In a double-blind placebo-controlled trial, co-ingestion of green tea polyphenols and L-theanine, an amino acid found in tea, was shown to improve memory and attention in subjects with mild cognitive impairment. Those subjects who consumed the supplement also displayed significantly increased theta brain wave activity as measure by electroencephalography (EEG); theta waves are associated with learning and memory.[271,272,273] Similar results were observed in animal models of cognitive impairment, and researches attributed some of the benefits to the free radical scavenging ability of green tea polyphenols.[274,275] Other research has shown that daily green tea supplementation attenuates age-related cognitive dysfunction in mice, even when treatment is initiated well into adulthood. These results suggest that green tea might protect neurons and preserve cognition regardless of age.[276]

Tea polyphenols and theanine may also ameliorate the damaging effects of amyloid-beta proteins, which accumulate in the brain as the hallmark pathology of Alzheimer's disease causing severe oxidative stress and neuronal death. Several animal studies have found that EGCG and related catechins suppress amyloid-beta induced cognitive dysfunction and neurotoxicity.[277,278,279]

Green tea supplementation has also been shown to optimize insulin signaling[280] and endothelial function,[281] which may provide additional neuro-protective benefits. Additional clinical trials have established that daily green tea supplementation favorably modulates multiple other metabolic parameters related to brain health, including body weight and lipid peroxidation.[282]

Resveratrol. Many researchers believe that at least some of the health benefits of red wine consumption may be due to its modest content of the well-known phenolic antioxidant molecule resveratrol. In addition to a multitude of evidence suggesting that resveratrol extends lifespan in experimental settings, likely by mimicking the genetic effects of calorie restriction,[283] numerous publications also highlight various roles for resveratrol in optimizing brain function.

Resveratrol may benefit the brain via mechanisms including increased synthesis of the growth factors IGF-1[284] and BDNF[285] in the hippocampus, suppressing formation of inflammatory metabolic products within the brain,[286,287] reinforcing the integrity of

the blood-brain-barrier,[288] and optimizing overall brain metabolism.[289] Other studies have shown that resveratrol supplementation preserves cerebrovascular integrity with aging,[290] and protects the brain after traumatic brain injury as well.[291]

In a double-blind, randomized, placebo-controlled human clinical trial, doses of resveratrol ranging from 250 – 500 mg were shown to dose-dependently enhance cerebral circulation and brain oxygenation.[292] In a trial involving non-human primates resveratrol supplementation was shown to increase physical activity levels and enhance both working and spatial memory. The investigators concluded that "*these results suggest that resveratrol could be a good candidate to mimic long-term CR effects and support the growing evidences that nutritional interventions can have beneficial effects on brain functions even in adults.*"[293]

B-vitamins

Inside the central nervous system B-vitamin-dependent reactions are responsible for ensuring the proper function of a vast array of neurochemical processes. When levels of B-vitamins, especially B6, B12, and folic acid, are insufficient to optimally support these reactions consequences such as impaired neurotransmitter synthesis and neurocapillary-damaging hyperhomocysteinemia can result.[294]

Multiple human studies have associated low plasma levels of B-vitamins, and even subclinical deficiencies, with cognitive decline and dementia.[295,296,297] Scott *et al* have shown that, in elderly patients, levels of folate correlate positively with the volume of the hippocampus and amygdala, and inversely with white matter hyperintensities, a marker of neuropathology observable upon MRI brain imaging.[298]

Figure 3: A mitochondrion; organelle within the cell within which chemical energy in the form of ATP is produced.

The brain may be the first organ affected by insufficient intakes of various other B-vitamins as well, including pantothenic acid, riboflavin, and nicotinamide, since these nutrients are important intermediaries in the mitochondrial oxidative phosphorylation (OXPHOS) process, a series of reactions by which chemical energy in the form of adenosine triphosphate (ATP) is produced. The brain produces more energy per unit mass than any other organ in the body, thus reflecting the sheer number of OXPHOS reactions taking place therein.[299,300,301]

Coenzyme Q10

A critical component of the OXPHOS reaction pathway, CoQ10 serves to shuttle electrons between two "stations" along the mitochondrial inner membrane on the pathway to ATP formation. Without adequate CoQ10 supply, electron transport may slow, resulting in fewer ATP molecules being produced, and ultimately less available cellular energy.

CoQ10 supplementation has been shown to improve outcomes in several neurodegenerative disorders involving loss of mitochondrial function, such as Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis.[302,303] Some animal data provides evidence for CoQ10's potential for preserving cognitive function in conditions such as experimental Alzheimer's disease.[304]

Inhibition of HMG-CoA by the widely-prescribed cholesterol lowing statin drugs is known to deplete levels of CoQ10 in the body. Indeed, studies have shown that co-administration of CoQ10 with statins may ameliorate some of the side effects of the drugs, and individuals with memory complaints who are also taking statin drugs may benefit from supplementation.[305,306,307]

Acetyl-L-carnitine

The amino acids lysine and methionine are biochemically conjoined *in vivo* to form the compound carnitine. Carnitine is essential for ensuring that fatty acids are transported into the mitochondrial matrix where they fuel aspects of OXPHOS, but under certain conditions, including age-related cognitive decline, endogenous synthesis may be insufficient to support optimal fatty acid transport. Subsequent to delineation of the role of carnitine in energy production, many researchers began to study the effects of supplementation with carnitine, and its more brain-permeable derivative acetyl-L-carnitine, upon various energy-demanding systems and reactions in the body.[308]

Supplementation with carnitine and acetyl-L-carnitine has been well-documented to ameliorate consequences of disease states with widespread implications for health, including type 2 diabetes and stroke.[309,310] However, more impressive is the efficacy of acetyl-L-carnitine in supporting brain health and cognition during normal age related cognitive decline and Alzheimer's disease. Acetyl-L-carnitine optimizes cognition by acting upon multiple facets of neuronal function, including enhancing efficiency of cholinergic neurotransmission,[311] stabilization of neuronal mitochondrial membranes,[312] increasing neural antioxidant defenses,[313] and enhancing neuron growth through sensitization to neurotrophic factors.[314,315]

A meta-analysis (comprehensive systematic review) of randomized, controlled human clinical trials involving data from 21 studies and data for over 1,200 subjects with mild cognitive impairment or mild to moderate Alzheimer's disease provides unequivocal evidence that supplementation with acetyl-L-carnitine ameliorates cognitive deficits observed during aging and during pathological brain deterioration.[316] The reviewers found that daily doses of acetyl-L-carnitine ranging from 1.5 – 3.0 grams consistently provided a statistically significant benefit over placebo for preserving cognition as assessed by multiple standardized tests. Moreover, there was a clear trend for a cumulative effect of acetyl-L-carnitine supplementation over time, suggesting that long-term use of acetyl-L-carnitine may provide the greatest benefit.

Phosphatidylserine

Like the omega-3's EPA and DHA, phosphatidylserine is an especially important component of cellular membranes. In the brain phosphatidylserine conjugates with DHA and helps maintain the proper electrical gradient along neuronal membranes, thus facilitating proper neural communication.[317] Human clinical trials have found that orally administered phosphatidylserine in doses ranging from 200 mg to 600 mg daily improves cognitive function in aging subjects with cognitive impairment.[318,319,320]

Ginkgo Biloba

The leaves of the Ginkgo biloba tree have been highly regarded throughout human history and used as a food additive and as a traditional medicine. Though widely regarded a nootropic, or cognitive enhancer, human clinical data as a whole suggests that supplementation with Ginkgo biloba extract alone, not in combination with other cognitive support ingredients, is minimally effective for improving cognitive function in those with Alzheimer's disease or cognitive impairment.[321] Nonetheless, because studies have shown that supplementation with ginkgo improves cerebral blood flow,[322] and other cerebrovascular-related aspects of cognition,[323] its use in combination with other brain-supporting nutrients may provide synergistic benefits for cognition. Indeed, results in both animals and humans suggest that, when ginkgo is combined with nutrients such as phosphatidylerine, B-vitamins, or vitamin E, the combination of ingredients confer cognitive benefits.[324,325] In fact, in one study comparing the effects of supplementation with Ginkgo biloba extract alone, to Ginkgo biloba extract together with phosphatidylserine, the combination of the two ingredients resulted in improvements in at least two aspects of memory performance, while Ginkgo alone did not. [326]

Bacopa Monnieri

In India, where the Bacopa monnieri herb grows, the leaves are held in high regard, and have long been believed in Ayurvedic medical tradition to promote cognitive health. More recently, modern scientific inquiry into the origins of these Ayurvedic tenets has revealed that the herb supports brain function through various mechanisms.

Bacopa is rich in free radical scavenging compounds including polyphenols and sulfur-based molecules, and so may ameliorate the oxidative stress generated by the brains' intense metabolic rate.[327] It also contains various phytochemicals with known anti-inflammatory properties, such as luteolin and apigenin.[328,329] Several human clinical trials have revealed cognitive-enhancing, and memory improving effects of supplementation with Bacopa extract.

In one double-blind, placebo-controlled trial, daily doses of 300 mg of Bacopa extract significantly improved visual information processing speed, memory consolidation, and lessened anxiety in healthy individuals after 12-weeks of supplementation.[330] Another double-blind, placebo-controlled study of the same duration, using the same dose of Bacopa extract, found that the benefits extend to elderly subjects as well. In this study, the group receiving Bacopa fared better on an auditory verbal learning test, and scored lower on anxiety and depression scales than those taking placebo.[331] Additional promising results were achieved in a similar study in which healthy adults received either 300mg of Bacopa extract daily, or a placebo, for 90-days. Improvements in working memory were noted in the Bacopa group, but not in the placebo group.[332]

Huperzine A

A compound derived from the plant Huperzia serrata, commonly known as clubmoss or firmoss, huperzine A is a well-established inhibitor of the *acetylcholinesterase* enzyme, a mechanism it shares with many commonly prescribed pharmaceutical treatments for Alzheimer's disease.[333,334] Inhibiton of acetylcholinesterase preserves levels of the neurotransmitter acetylcholine, which is critical for cognition and memory.

Huperzine A has been shown to enhance memory in healthy young humans,[335] and in a recent comprehensive literature review, it was found that high doses of huperzine A significantly improved scores on standardized cognitive tests achieved by patients with Alzheimer's disease in a time-dependent manner.[336]

Lion's Mane (*Hericium erinaceus*)

Hericium erinaceus (lion's mane mushroom) is an edible and medicinal mushroom that has been used traditionally in Asia to improve memory.[489-491] Some of the major beneficial components found in this mushroom include beta-glucan polysaccharides; erinacine A, C, S; and sesterterpene.[491,492] Several laboratory and animal studies reported that compounds from *H. erinaceus* have lipid-lowering, antioxidant, anti-hypertensive, neuroprotective, anti-tumor, antibacterial, and immune-stimulating effects.[489,491,493]

In a double-blind placebo-controlled clinical trial, Japanese men and women between 50 and 80 years who had been diagnosed with mild cognitive impairment received 250 mg *H. erinaceus* tablets containing 96% of the mushroom dry powder three times daily for 16 weeks. After eight weeks, the *H. erinaceus* group exhibited better cognitive scores than the placebo group, and the improvement continued through the supplementation period.[494]

In a mouse model of Alzheimer's disease, 30 days of oral administration of an *H. erinaceus* extract reduced the production and deposition of amyloid in animals' brains and supported the growth of brain cells. Longer-term administration, for five months, helped recover cognitive decline in the same study.[495] The benefits of *H. erinaceus* extracts for cognition are supported by other studies on mouse models of Alzheimer's disease, which found that the extract improved nerve cell formation, decreased cellular

damage, and recovered some of the animals' behavioral deficits.[492] In another study on mice with Alzheimer's disease, a *H. erinaceus* extract increased serum and brain levels of the neurotransmitter acetylcholine, levels of which decline in Alzheimer's disease.[496-498] In rats with neuronal injury, an aqueous extract of *H. erinaceus* promoted the regeneration of peripheral nerves.[499]

In a different mouse model,supplementation with a *H. erinaceus* extract blocked inflammatory signaling and reversed the depression-like behavior caused by stress.[500] These findings are significant, considering that up to 50% of Alzheimer's patients experiencedepression.[501-503] Benefits have also been observed in healthy mice, in which oral supplementation with a *H. erinaceus* extract improved recognition memory and neurotransmission in a brain area involved in cognitive function and emotions.[504]

Laboratory studies revealed that extracts or compounds isolated from *H. erinaceus* support neuronal growth and survival.[489] An *H. erinaceus* water extract was neuroprotective in laboratory experiments and decreased the accumulation of reactive oxygen species inside cells.[496]

Glyceryl Phosphoryl Choline

Glyceryl phosphoryl choline (GPC) is a form of choline that is naturally present in all the body's cells. Among aging adults, the rationale for GPC therapy goes back to the hypothesis, developed more than 30 years ago, that declining levels of acetylcholine —and a concurrent decrease in the number of neurons that are its intended target—are responsible for a range of cognitive deficits.[337] Acetylcholine is an essential neurotransmitter involved in muscle control, sleep, and cognition. Research has shown that GPC is a precursor of acetylcholine that is safe and well tolerated.[338] A review of 13 published studies, involving more than 4000 participants, found that patients taking GPC exhibited neurological improvement and relief of clinical symptoms of chronic cerebral deterioration that was clearly superior to placebo and "*superior or equivalent*" to that obtained with prescription drugs. The same authors found that GPC was superior to choline and lecithin and that it deserved wider study as a therapy for stroke patients seeking to regain full cognitive function.[339]

Vinpocetine

A semisynthetic derivative of the lesser periwinkle plant (*Vinca minor*), vinpocetine has been shown to exert a variety of biological effects that may benefit brain health. It is known to regulate the action of sodium in neurons, lessening the damaging effects of hypoxia as seen in stroke, as well as mitigating oxidative stress.[340] Vinpocetine also blunts the activity of an enzyme called *phosphodiesterase type 1,* an effect which may increase neuronal energy by up-regulating the energy "throttle" *cyclic AMP.*[341] Also, vinpocetine itself has demonstrated the ability to neutralize particularly damaging hydroxyl radicals.[342] Moreover, vinpocetine supports healthy blood flow by enhancing vasodilation and blunting platelet aggregation, effects which may enhance cerebral circulation.[343,344] Indeed, human clinical trials show that large doses of IV vinpocetine, followed by three months of oral supplementation with 30 mg vinpocetine, eases blood flow in patients with chronic cardiovascular disease.[345]

Multi-Vitamin

Even the healthiest diets may not provide the optimal levels of micronutrients, vitamins, and minerals needed to support healthy brain function. A comprehensive multi-vitamin supplement may help to fill these nutritional gaps and ameliorate some consequences of insufficient dietary nutrition. In a double-blind, controlled clinical trial involving over 200 healthy middle-aged individuals subjects were given either a multi-vitamin or placebo for more than two months, and both groups were then assessed for cognitive function. It was shown that those taking the multi-vitamin displayed less fatigue during extended cognitive challenges, and were also more accurate. Also, those taking multi-vitamins were able to more quickly complete mathematical processing tests than subjects receiving placebo.[346]

Magnesium-L-Threonate

Age-related cognitive decline is associated with reduced synaptic plasticity in the brain. A novel form of magnesium, magnesium-L-threonate, has been shown to enhance signaling through pathways that promote synaptic plasticity.[347] Also, Alzheimer's disease is associated with magnesium deficit and accumulation of amyloid-beta plaques in the brain.[348] Magnesium-L-threonate has been shown to boost brain magnesium levels and enhance the clearance of amyloid-beta in preclinical and laboratory research.[349,350] In a mouse model of Alzheimer's disease, treatment with magnesium-L-threonate reduced amyloid-beta accumulation, prevented synapse loss, and reduced memory decline. Magnesium-L-threonate conferred benefit even when given to mice with advanced-stage Alzheimer's-like disease.[351] This novel magnesium compound was also shown to combat inflammatory processes in the brain by preventing upregulation of the inflammatory mediator TNF-α.[350]

Pyrroloquinoline Quinone (PQQ)

Pyrroloquinoline quinone, or PQQ, is a highly bioactive compound present in a vast range of cell types, and research suggests boosting PQQ levels may improve mitochondrial function, inhibit oxidative stress, and support neurological health.[366-371]

Research indicates PQQ is a neuro-protectant that can promote nerve repair. A number of laboratory and animal studies indicated PQQ can protect nerve cells from toxic and inflammatory damage by reducing oxidative stress and protecting mitochondria.[372-375] In a study in rats exposed to high levels of oxidative stress, PQQ supplementation protected against

memory loss.[376] Several studies showed PQQ may prevent the accumulation of damaging amyloid proteins, which might protect against conditions such as Alzheimer's disease and Parkinson's disease.[377-380] PQQ has also been found to stimulate the production of a protein called nerve growth factor and promote the regeneration of nerves in animals.[381-384]

In two clinical trials, PQQ increased regional brain blood flow and oxygen use, resulting in improved cognitive function. In 41 healthy elderly subjects, 20 mg PQQ daily for 12 weeks resulted in higher cognitive test scores compared with placebo. In addition, scores on visual/spatial cognitive tests improved significantly in those receiving PQQ that had the lowest scores at the beginning of the trial. Near-infrared spectrometry results also suggested PQQ supplementation increased cerebral blood flow.[370] Another study using near-infrared spectrometry confirmed taking 20 mg PQQ daily for 12 weeks led to increased regional brain blood flow and oxygen utilization in healthy subjects.[385]

Nicotinamide Riboside

Nicotinamide riboside is a source of vitamin B3 that the body uses as a precursor for nicotinamide adenine dinucleotide (NAD), a molecule involved in a range of critical biological processes.[386] NAD+, a biologically active form of NAD, is necessary for the activation of sirtuins, proteins that modulate cellular metabolism and DNA transcription.[386-388] NAD+-dependent sirtuins appear to be involved in essential cellular activities including energy metabolism, DNA damage response, stress resistance, proliferation and differentiation, survival, and aging,[389] and in animal research have been shown to be involved in brain connectivity and memory formation.[390] NAD+ levels decrease with age, which may cause dysfunction in cell nuclei and mitochondria, ultimately contributing to age-related disorders including cognitive decline.[388,389] Restoration of NAD+ with supplemental nicotinamide riboside has been shown to reverse age-related cellular dysfunction, which contributes to many neurodegenerative diseases, while models of neurodegenerative disease indicate nicotinamide riboside may be neuroprotective.[386,388,391-393]

In a six-month controlled clinical trial in 26 individuals with probable Alzheimer's disease, those who received the NADH form of nicotinamide adenine dinucleotide had no progression in cognitive decline and significantly better scores on a dementia rating scale compared with the placebo group.[394] In rodents, NADH administration in older animals resulted in improved performance on cognitive tests.[395] In a mouse model of Alzheimer's disease, three months of nicotinamide riboside supplementation led to increased brain levels of NAD+, prevented cognitive decline, and reduced production of neuron damaging amyloid-beta proteins.[396]

Lithium

Lithium is a mineral used as a mood stabilizer, particularly in the treatment of bipolar disorder and major depression.[397] Animal and laboratory research indicate lithium may have neuroprotective effects and may preserve cognitive function in models of cognitive decline and Alzheimer's disease.[398-401] In humans, lithium appears to increase brain mitochondrial functioning, reduce brain oxidative stress and markers of inflammation, promote production of BDNF, and benefit areas of the brain involved in memory and cognitive activities.[397,402]

Lithium supplementation may enhance cognitive function.[403,404] Early evidence from animal and human studies suggest lithium may be protect against cognitive losses associated with ischemic stroke, cancer treatment, and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease.[405-408] In a pilot study, patients with Alzheimer's disease treated with 300 micrograms lithium per day (at least 3000 times lower than typical doses used to treat bipolar disorder) for 15 months experienced no changes in cognitive performance, while their untreated counterparts experienced significant cognitive losses.[409] In a pilot trial in 45 subjects with amnestic mild cognitive impairment (a condition that frequently progresses to Alzheimer's disease), those who received lithium performed modestly better on some cognitive function tests over a 12-month period compared with placebo, although this difference was small and not statistically significant.[410]

Findings from animal studies suggest the positive effects of lithium on memory and cognitive function may be enhanced by the simultaneous use of zinc or pyrroloqinoline quinone.[411,412]

The neuroprotective effect of lithium appears to be related to its ability to inhibit an enzyme known as glycogen synthase kinase 3 (GSK-3). This enzyme catalyzes reactions that join phosphates to proteins called tau proteins. Overly phosphorylated tau proteins aggregate and form the basis of the neurofibrillary tangles correlated with cognitive decline in Alzheimer's disease.[413-415] By inhibiting GSK-3, lithium helps regulate tau protein phosphorylation and prevent neurofibrillary tangle formation.[413] GSK-3 inhibition has also been associated with reduced amyloid production.[416,417] Furthermore, animal and laboratory research show lithium treatment may increase brain levels of a neuroprotective protein called beta-cell lymphoma 2 (Bcl-2).[418]

Because doses of lithium used to treat bipolar disorder (typically 900–1800 mg per day) are well known to cause a number of side effects,[419] including kidney toxicity and brain cerebellar toxicity and atrophy (shrinking),[420,421] researchers have been monitoring the effects of long-term use of lower doses. A preliminary, randomized, controlled trial in 61 older subjects with mild cognitive decline receiving low-dose lithium found no significant evidence of kidney damage after four years of treatment; however, lithium-treated subjects had higher incidence of weight gain, decreased thyroid function, new-onset diabetes, and abnormal heart rhythms. The lithium doses used in this study were ≥ 150 mg per day, and individualized to maintain serum levels

between 0.25 and 0.50 mmol/L.[422] While lithium appears to hold potential for people with cognitive decline, these findings point to more research needed to determine ideal dosing and long-term safety.

Colostrinin (Proline-rich peptide complex)

Colostrum—the first breast milk secreted after childbirth—is known for its high levels of antibodies and other factors with immune-activating effects.[423] Findings from preclinical and clinical studies suggest colostrinin, a proline-rich polypeptide complex in colostrum, may help prevent the progression of cognitive decline, particularly in people with Alzheimer's disease.[424,425] A number of studies have found a range of possible mechanisms for colostrinin's beneficial effects, including modulating immune activity; preventing oxidative stress, including oxidative damage to DNA; anti-inflammatory activity; inhibiting overproduction of nitric oxide; and decreasing age-related mitochondrial dysfunction.[426-431]

A double-blind placebo-controlled trial compared colostrinin to placebo in 105 subjects with mild-to-moderate Alzheimer's disease. The colostrinin group received 100 micrograms colostrinin every other day for three weeks, followed by two weeks with no treatment, for three 5-week cycles. After the first 15-week period, all subjects received colostrinin for a second 15-week treatment cycle. Colostrinin treatment had a stabilizing effect on cognitive function and ability to perform activities of daily living. Participants with mild cognitive impairment responded better to treatment than those with more advanced decline.[432] Another trial used the same dosing schedule for 16 to 28 months in 33 Alzheimer's patients and found it resulted in stabilization or improvement in health status.[433] An earlier double-blind placebo-controlled trial was conducted in 46 patients with Alzheimer's disease and mild-to-moderate dementia. Subjects received either 100 micrograms colostrinin, 100 micrograms selenium, or placebo every other day in three-week treatment cycles, followed by two weeks of no treatment. Eight of 15 colostrinin patients improved, while seven of them experienced stabilization of their condition; in contrast, none of the patients in the selenium or placebo groups improved.[434] Studies reported colostrinin was well tolerated with mild side effects that passed quickly.[433,434]

Studies in which cultured nerve cells were treated with colostrinin or a nanopeptide fragment of colostrinin have demonstrated their potential to disrupt amyloid beta fibrils and prevent further accumulation and neurotoxic effects of amyloid beta.[435-438]

Cocoa

Cocoa has been consumed by humans for thousands of years,[439] and its medicinal use has been documented for hundreds of years.[440] Modern research shows cocoa and chocolate have powerful brain-boosting benefits.

A study in 309 subjects age 65 assessed the association of chocolate intake and cognitive decline, with a median follow-up of four years. In individuals whose caffeine intake was less than 75 mg per day (roughly the amount in a six ounce cup of coffee or two cups of tea),[441] those who consumed chocolate had a 50% reduced risk of cognitive decline.[442] Another study in 968 adults found higher chocolate consumption was correlated with better performance on cognitive function tests.[443]

A double-blind clinical trial has shown that cocoa consumption can support healthy blood flow in the brain and support cognition. Sixty adults with an average age of 73 and high blood pressure and/or well-controlled type II diabetes consumed two cups of a cocoa drink daily for 30 days. All subjects had their neurovascular coupling and cognitive function measured at baseline and on days 1 and 30 after beginning the cocoa consumption. After 24 hours, subjects with impaired *neurovascular coupling* at baseline had a 10.6% improvement, and by day 30, these subjects' performance on a test requiring attention significantly improved. The baseline time to complete this test was 167 seconds versus 116 seconds at day 30.[444]

Spearmint Extract

Spearmint (*Mentha spicata*) is an aromatic herb used traditionally to enhance memory and cognition.[445] It is rich in water-soluble polyphenols, many of which have anti-inflammatory and free radical-reducing properties. Rosmarinic acid and its derivatives generally appear to make up the greatest proportion of spearmint's polyphenols.[446] Spearmint and rosmarinic acid have been found to inhibit enzymes that break down neurochemicals involved in learning, memory, and mood.[445,447-448]

In one trial, 11 subjects with self-reported mild memory impairment were given 900 mg of high-rosmarinic acid spearmint extract per day for 30 days. At the end of the treatment period, performance on tests of reasoning, attention, and concentration improved significantly. Even short-term administration resulted in improvements in attention and concentration within 2–4 hours.[449]

In animal studies, rosmarinic acid demonstrated neuroprotective properties[450,451] and improved cognitive function.[447,452] In one such study, mice with an experimental form of age-related cognitive impairment exhibited better memory and learning, and had less evidence of brain tissue oxidation, after treatment with a spearmint extract containing 5% rosmarinic acid.[453]

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protocol listed on this website. The protocols described on this website are for adults only, unless otherwise specified. Product labels may contain important safety information and the most recent product information provided by the product manufacturers should be carefully reviewed prior to use to verify the dose, administration, and contraindications. National, state, and local laws may vary regarding the use and application of many of the treatments discussed. The reader assumes the risk of any injuries. The authors and publishers, their affiliates and assigns are not liable for any injury and/or damage to persons arising from this protocol and expressly disclaim responsibility for any adverse effects resulting from the use of the information contained herein.

The protocols raise many issues that are subject to change as newdata emerge. None of our suggested protocol regimens can guarantee health benefits. The publisher has not performed independent verification of the data contained herein, and expressly disclaim responsibility for any error in literature.

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