Grey Matters, Minding Brain Health

By Erika Camardella, Associate Editor

When it comes to the science of the brain, there is quite a bit of grey matter. But as Lyall Watson, Ph.D., naturalist and author of “Supernatural” eloquently said, “If the brain were so simple we could understand it, we would be so simple we couldn’t.”

Amazing that a bundle of neurons innervate the body to perform the miracle of cognition and such abstract concepts as reasoning, perception, intelligence, learning, comprehension, decision-making and planning. We can contemplate and have power to argue such mysteries as the expanding/contracting universe, negative matter and life; it’s no wonder the organ that houses such musing is a phenomenon unto itself.

Medicare currently spends nearly three times as much for people with Alzheimer’s and other dementias than for the average Medicare beneficiary. These costs are projected to double from $91 billion in 2005 to more than $189 billion by 2015, more than the current gross national product of 86 percent of the world’s countries, according to the Alzheimer’s Disease Facts and Figures report (2007, alz.org). In 2005, state and federal Medicaid spending for nursing home and home care for people with Alzheimer’s and other dementias was estimated at $21 billion; that number is projected to increase to $27 billion by 2015.

According to Maryellen Molyneaux, president of The Natural Marketing Institute (NMI), nearly three-quarters of consumers are using supplements, foods or beverages to prevent memory problems.

Cognitive dysfunction is oft taken for granted, treated as an expected part of “getting old”. Yet, in research terms, there is no link between progressive cognitive decline (usually noticeable in middle age) and cognitive dysfunction, only that decline is more likely as we age.

That said, one icon stigmatizing any range of memory decline—**Alzheimer’s disease** (AD)—has become a societal concern. The Alzheimer’s Association reports there are now more than 5 million people in the United States living with Alzheimer’s disease (2007), and unless a cure or effective treatment to delay the onset or progression of the AD is found, the prevalence could soar to 7.7 million people by 2030. Two types of abnormal lesions—beta-amyloid plaques and neurofibrillary tangles—clog the brains of individuals with AD, building up inside the nerve cells. Although these are hallmarks of the disease, scientists are unclear whether they cause it or are a byproduct of it.

Parkinson’s disease (PD) and **Huntington’s disease** are also conditions that affect cognitive function. Symptoms of both include memory loss, impaired coordination, uncontrolled movements and dementia; however, Huntington’s disease, the rarest of the three diseases, results from a genetically programmed degeneration of neurons, while PD results from a combination of genetic susceptibility and exposure to one or more environmental factors that trigger the disease (ninds.NIH.gov).

Fortunately, there is some hope on the horizon. Numerous controlled clinical trials have demonstrated improved brain performance from dietary supplementation with specialty nutrients. Scientists have demonstrated several nutritional building blocks to properly benefit the moods and minds of men and women to maximize the potential of this three-pound cognitive control tower of the central nervous system.

Offsetting Oxidation Effects

Oxidation is the culprit behind the breakdown of most tissues, and brain tissue, with its high metabolic rate and high content of polyunsaturated lipids, is particularly susceptible to peroxidative attack. Free radical accumulation and oxidative stress may contribute to the progression of motor neuron disease. **Antioxidants**, including **carotenoids**, **vitamins C a**nd **E**, **selenium**, methionine and acetylcysteine, assist in maintaining brain integrity by countering cognitive decline, particularly in the elderly. Boston researchers reported an antioxidant-rich diet may preserve cognitive ability, as oxidative damage decreased motor and cognitive performance, and increased the possibility of neurodegenerative diseases including amyotrophic lateral sclerosis (ALS), AD and PD.[1]

Italian researchers have also found connections between depressed peripheral levels of the antioxidants vitamin C, vitamin A and vitamin E, and carotenoids (lutein, zeaxanthin, beta-cryptoxanthin, lycopene, alpha-carotene and beta-carotene); and activities of plasma and red blood cell (RBC) antioxidant enzymes such as **superoxide dismutase (SOD)** with mild cognitive impairment (MCI) and AD in test subjects, compared to controls.[2] They also noted MCI may represent an early symptom stage of AD, and since oxidative damage appears to occur as one of the earliest pathophysiological events in AD, an increased intake of antioxidants could be helpful in lowering the risk MCI evolving to dementia. And a clinical trial out of Washington provides additional research behind taking antioxidant supplements to ensure top cognitive performance over a lifetime.[3] Researchers monitored long-term antioxidant status and cognitive function in a seven-year study of 2,082 community-dwelling elderly subjects and found that those subjects who supplemented with vitamins A, C or E, plus selenium or **zinc**, had a 34-percent lower risk of developing cognitive impairment and a 29-percent lower risk of experiencing cognitive decline, compared with non-antioxidant users.[4]

On its own, vitamin E is critical in the neuroprotective antioxidant category—with impressive efficacy against AD and other neurodegenerative disorders.[5,6] Japanese researchers found chronic lipid peroxidation due to alpha-tocopherol depletion enhanced AD phenotype in a mouse model.[7] Another study out of the University D'Annunzio, Chieti Scalo, Italy, measured motor nerve conduction velocity of the right superficial peroneal nerve using a standard neurophysiologic technique in a population-based sample of subjects aged between 20 and 103 years old enrolled in the InCHIANTI study.[8] They concluded inflammation and inadequate antioxidant defenses are associated with accelerated decline of nerve conduction velocity over the aging process.

Clinical studies support the idea that vitamin E may have a key role to play in brain health. A six-year study out of Rush University, Chicago, found a correlation between cognitive decline and intakes of vitamin E, alpha-tocopherols and alpha-tocopherol equivalents, and gamma-tocopherols.[9] Italian researchers found, in a cohort of 1,033 elderly people, those individuals with plasma vitamin E levels in the bottom tertile had a significantly higher probability of being demented and suffering from cognitive impairment, compared to those in the highest vitamin E tertile.[10]

In addition, vitamin E's **tocotrienols** may be even more effective than its tocopherols. Nanomolar alpha-tocotrienol, not alpha-tocopherol, is potently neuroprotective,[11] and crosses the blood-brain barrier.[12] Researchers at The Ohio State University Medical Center, Colombus, observed micromolar, but not nanomolar, alpha-tocotrienol functions as an antioxidant, as verified in a model involving linoleic acid-induced oxidative stress and cell death.[13]

Two studies on natural full-spectrum palm tocotrienols, funded by the National Institutes of Health (NIH) and led by Chandra K Sen, M.D., Ohio State University Medical Center, found oral tocotrienols (as Tocomin® and Tocomin® SupraBio™, from Carotech Inc.) were effective in elevating blood plasma levels to concentrations that could help protect against neurological damage resulting from stroke.[14] In the first study, a group of women were given 400 mg of Tocovid SupraBio soft gel capsules; blood samples were collected at 2, 4, 6 and 8 hours after supplementation. Peak plasma tocotrienol levels were found to be 12 to 30 times higher than those needed to completely prevent stroke-related neurodegeneration as determined by earlier research. In the second study, Sen's team determined tocotrienols protect against stroke-induced neurodegeneration by acting as an antioxidant at higher concentrations, and providing non-antioxidant protection at lower levels,[15] although higher concentrations of tocotrienols were needed to reduce free-radical activity and resulting neurotoxicity.

Another vitamin-like compound, coenzyme Q10 (CoQ10), is a powerful antioxidant that buffers the potential adverse consequences of free radicals produced during oxidative phosphorylation in the inner mitochondrial membrane.[16] As CoQ10 levels decline with age,[17] accelerating precursors of beta-amyloid deposition, CoQ10 supplementation may be preventive against AD, PD and other neurodegenerative disorders.[18] For example, in one study, CoQ10 therapy attenuated amyloid betapeptide toxicity in brain mitochondria isolated from elderly rats.[19] Hong Kong researchers similarly found in a group of 48 mice (four genotypes), those treated with CoQ10 (1,200 mg/d) for 28 days after ischemic injury for 28 days had amyloid precursor protein mutations had smaller infarct volumes, while the volumes of hemisphere and hippocampus on the infarcted side were larger than those treated with placebo, suggesting CoQ10 could protect the brain from ischemic-related atrophy in aged and susceptible transgenic mice.[20] The combination of CoQ10 with vitamin E may also be beneficial, as research from the University of North Texas, Fort Worth, showed supplementation of aged mice with CoQ10 and alpha-tocopherol improved brain function, as measured by cognitive tests.[21]

Fruits and vegetables are rich sources of multiple antioxidants, leading many suppliers and researchers to explore the benefits extracts of these foods may provide. A study out of the Human Nutrition Research Center on Aging at Tufts, Boston investigated the impact of a multi-berry extract (as OptiBerry®, from InterHealth Nutraceuticals) fed to Fischer rats for eight weeks, was effective in reversing age-related deficits in several neuronal and behavioral parameters, including Morris water maze performance.[22] Boston researchers similarly found diets supplemented with spinach, strawberries or blueberries (nutritional goldmines for antioxidants) given to aged rats, could reverse age-induced declines in beta-adrenergic receptor function in cerebellar Purkinje neuron and improved motor learning, critical for rehabilitation following stroke, spinal cord injury, and the onset of some neurodegenerative diseases.[23] And spirulina may be even more powerful, as an in vitro study found it could reduce brain damage caused by ischemia by roughly 70-percent; blueberries and spinach reduced it by 30 percent.[24]

The carotenoid **astaxanthin** also has brain-protective abilities, which may be due in part to its ability to cross the blood-brain barrier.[25] A series of tests conducted at the International Research Center for Traditional Medicine, Japan, found mice fed astaxanthin (as Bioastin, Cyanotech Corp.) one hour before induction of ischemia (arterial obstruction of blood to the brain) performed better in a maze designed as a learning performance test.[26] The researchers concluded: "The present results showed astaxanthin had neuroprotective effects at relatively high doses by preventing the ischemia-induced impairment of spatial memory in mice." Japanese researchers did further work in this area in a rat model. Rats were fed Astaxanthin twice before inducing ischemia; and once after releasing blood flow. Rats were killed and brains were compared with a control group fed olive oil. Researchers found that the rats fed Astaxanthin had 40-percent less brain damage than control.[27]

Fat's Where It's At

The function of fatty acids is largely dependent on the state of the lipid membranes in which they are found, and half the dry weight of the brain is lipid and half of the lipid portion consists of **essential fatty acids (EFAs)**. The quantity and strength of evidence for effects of omega-3 fatty acids on the neurological conditions assessed vary greatly.[28]

However, people who eat fish or fish supplements score 13-percent higher in IQ tests and are less likely to show signs of AD.[29] And cohort studies from Holland,[30] France,[31] and the United States[32] demonstrated lower risk of developing dementia in people with a regular intake of seafood compared to non-fish eaters.

Clinical trials are investigating the role of dietary and supplemental EFAs on brain function. One large-scale clinical, funded by NIH and led by the director of the National Institute on Aging (NIA) is evaluating whether the omega-3 fatty acid **DHA (docosahexaenoic acid**, as life'sDHA™, from Martek Biosciences Corp.), taken over many months, slows the progression of both cognitive and functional decline in people with mild to moderate AD.

However, completed studies have confirmed the protective and even preventive effect of DHA or its metabolites. A study out of the Karolinska Hospital in Stockholm, Sweden demonstrated that patients given an omega-3 concentrate high in DHA (as EPAX 1050G, from EPAX AS) halted further memory decline while patients on placebo continued to deteriorate[33] The 204 patients, in early stage AD, were randomly given EPAX 1050 TG (4 g/d), or placebo (corn oil) for six months; the placebo group then was also given the EPAX supplement. All patients were also treated with acetylcholine esterase inhibitors, a standard AD treatment. The patients on active treatment did not demonstrate significant progression of memory decline; the placebo group had a two-point memory decline in six months, until switched to EPAX treatment, at which point memory decline was arrested. "We are now starting to realize the importance of DHA in the brain as being not only a structural component of brain cells, but moreover, a natural compound guarding the aging brain cells from degradation by neurotoxic mechanisms," said Yvonne Freund-Levi, M.D, and lead researcher in the study.

The mechanism of EFA supplements in brain health is under investigation as well. Recently a neuroprotective effect of DHA has been demonstrated in an animal model of brain damage.[34] Other experiments, with transgenic mice developing neuron amyloid resembling human amyloid deposition in brain cells leading to AD, have provided better understanding of the pathophysiology of the

diseases. One study demonstrated a protective effect of DHA on brain cell death.[35] Another study showed positive effects in the prevention of amyloid formation in the mouse brain.[36]

Another fatty compound with brain protective properties is **citicoline**. Citicoline is involved in maintaining the structural integrity and functionality of neuronal membranes and is a precursor of the neurotransmitter, acetylcholine (Ach). A meta-analysis out of Rome confirmed citicoline has a positive effect on memory, at least in the short to medium term; the researchers noted the evidence for this theory was limited only by the duration of the studies reviewed.[37]

In a 2004 review, conducted by Richard Conant, MAc, CN, and Alexander G. Schauss, Ph.D. at the American Institute for Biosocial and Medical Research, Inc. (AIBMR), Puyallup, WA found that as a dietary supplement, citicoline appears useful for improving both the structural integrity and functionality of the neuronal membrane that may assist in membrane repair in older subjects.[38]

In a recent unpublished study, the effect of citicoline (as Cognizin™, from Kyowa Hakko USA) on the memory performance was examined in mice. Forty (eight-week old) mice were subjected to training in a Morris water maze to learn how to reach the platform (PF). After 18 training “sessions”, almost all the mice could reach the PF within 20 seconds. The mice were then randomly divided into two groups. Commercial diet (CE2) was given to one group (control), and a CE2 diet containing two percent citicoline was given to another group for four weeks, without any training. After the completion of the feeding period, the mice were forced to swim in the Morris water maze for one minute without PF. Results showed the time for reaching and crossing over the former PF position was found shorter in the mice given citicoline than in the control mice; and the mice given citicoline, had increased frequency of crossing-over at the former PF position within 60 seconds compared with the control mice.

“Additional studies point to the ability of Cognizin to act as an antioxidant in preserving normal healthy visual function. In addition, Cognizin protects neural tissue from the ravages of free radical damage,” said Toshi Kamiya, research director at Kyowa Hakko.

In vivo proton magnetic resonance spectroscopy (1H-MRS) was used to measure brain levels of cytosolic, choline-containing compounds before and after single oral doses of cytidine 5' diphosphate choline (CDP-choline).[39] Results suggest that the cytidine moiety of CDP-choline stimulates phosphatidylcholine synthesis in human brain cell membranes in older human subjects.

Once sold as a prescription drug and over-the-counter (OTC) for fighting cognition impairment, **phosphatidylserine (PS)** is a natural phospholipid derived from both plant (soy) and animal (bovine) sources. Soy-derived PS has been validated through double blind trials for improving memory, learning, concentration, word recall, and mood in middle-aged and elderly subjects with dementia or age-related cognitive decline.[40] It is active in cell membranes, and is a major building block for nerve cells. In a study out of England, young adults (with neuroticism scores above rather than below the median) given 300 mg/d PS for a month were less stressed and had a better mood.[41]

In a double blind, randomized, placebo-controlled study with PS, published in Neurology journal,[42] 149 subjects, aged 50 to 75 years were given PS at 300 mg/d for 12 weeks. There was significant improvement in learning and recalling names, faces, telephone numbers, misplaced objects, paragraphs and the ability to concentrate.

Chemi Nutra's SerinAid® PS was evaluated in an unpublished research study at the University of Guadalajara in Mexico, involving PS and its ability to reduce the incidence of memory loss that accompanies hormone replacement therapy (HRT) in women. In the final report, the researcher commented that PS "improved various emotional aspects" related to HRT.

Botanical Brain Boosters

Nutritional and botanical therapies are available offering proven degrees of efficacy and generally favorable benefit-to-risk profiles. **Vinpocetine, Bacopa monniera (Bacopa**) and **Ginkgo biloba** extract are a handful of nature's offerings with interesting contributions to a personalized approach for restoring cognitive function.

Vinpocetine is a chemical substance isolated from vincamine, a vinca alkaloid obtained from the leaves of the Lesser Periwinkle (Vinca minor). It was discovered in the late 1960s, and has been used by humans for over 20 years. Studies in humans and in animal models demonstrate vinpocetine's ability to increase short-term memory and increase critical reaction time in healthy volunteers.[43] It increases blood flow to the brain through reduction in flow resistance of cerebral vessels,[44] and improves the rheological properties of blood by inhibiting platelet aggregation and increasing the deformability of red blood cells of erythrocytes.[45]

Bacopa (Bacopa monniera, BM) or water hyssop, is the source of a centuries-old plant extract with specific cognition-enhancing benefits. This Ayurvedic botanical has apparent anti-anxiety, anti-fatigue and memory-strengthening effects.[46,47,48] An Indian study showed administration of BM extract to mice with cognitive impairment induced by phenytoin improved the animals' scores on a passive avoidance test.[49] An unpublished study out of Oregon State University concluded Bacopa extract (as BaCognize®, from Verdure Sciences) displaced antagonist [3H] Ketanserin from serotonin receptor 5HT2a isolated from rats, and exhibited even stronger effects in its displacement of agonist 8-OH-DPAT from the 5HT1a receptor—indicative of its strong serotonin receptor activity.

Ginkgo biloba extract a Chinese botanical, is widely used in the treatment of acute ischemic stroke in China and is also used occasionally in Europe. Studies on ginkgo have generally shown positive results. Polish researchers, for example, reported preventive doses of 100 mg/kg ginkgo (as EGb 761, from Willmar Schwabe Group) in rats prior to a two-hour episode of restraint stress or corticosterone injection, abolished cognitive deficits as measured by decreased re-entry latencies in a passive avoidance test.[50] Further, another study by the same researchers showed 100 mg/kg doses of EGB 761 improved spatial and nonspatial memory in the Morris water maze and object recognition tests in chronically stressed or corticosterone-treated rats.[51] And ginkgo's positive effects on spatial learning and memory have been demonstrated by two studies from China.[52,53]

On another note from nature, a variety of **green oat** (Avena sativa L.) may help cognitive function. Unpublished studies conducted on Avena sativa (as Neuravena ™, from Frutarom) suggest it has activity on two cerebral enzymes closely connected to mental health and cognitive function. In vivo, quantitive analysis demonstrated Neurovena has stimulating properties and the dopaminergic transmitter system—implicated in cognitive functioning and depression.

Soy has been shown to promote cognitive wellness, especially among postmenopausal women, although results have been mixed. In one study, daily supplementation with 80 mg soy-derived

isoflavones did not improve performance on standard neuropsychological tests and overall quality of life in generally healthy Chinese postmenopausal women.[54] However, in another six-month, double blind, randomized, placebo-controlled clinical, researchers concluded 55 mg/d of soy-extracted isoflavones (as Soyselect, from Indena) supplementation has a favorable effect on cognitive function, particularly verbal memory, in postmenopausal women.[55]

Adding to the list of botanicals, **ginseng** root, a Chinese adaptogenic herb, may also have cognitive-enhancing effects. Supporting this is a double blind, placebo-controlled, crossover study out of England, which showed administration of Panax ginseng to healthy young adults subjected to a 10-minute test battery at baseline, and then six times in immediate succession after receiving ginseng extract or placebo.[56] Researchers found ginseng produced significant reductions in blood glucose levels at all three post-treatment measurements; and concluded ginseng can improve performance and subjective feelings of mental fatigue during sustained mental activity, possibly due to acute gluco-regulatory properties of the extract.[57] And an in vitro study showed ginsenosides enhanced neurite outgrowth in the absence of a nerve growth factor.[58]

And **Ashwagandha (Withania somnifera**), an Ayurvedic botanical used in India, is another adaptogenic herb thought to benefit neurons' dendrites and axons (where input is received and released) damaged by neurodegeneration.[59] Researchers at the Toyama Medical and Pharmaceutical University in Japan concluded ashwagandha promotes the formation of dendrites, which may compensate for and repair damaged neuronal circuits in the dementia brain. Additional studies from the same institution found oral administration of withanoside extracted from ashwagandha significantly improved memory deficits in beta-amyloid-injected mice, and prevented loss of axons, dendrites, and synapses in the cerebral cortex and hippocampus.[60,61]

Resveratrol, the polyphenolic phytoalexin phenomenon found in grape skins, is another botanical brain booster. Resveratrol may protect against the ravages of ischemia in the brain; researchers from National Chia- Yi University gave 60 adult male rats general anesthesia and randomized them to receive an ischemia treatment (bilateral ligation of carotid artery), ischemia combined with resveratrol administration (20 mg/kg) or a sham treatment.[62] In rats not administered resveratrol, hydroxyl radical levels were elevated and severe neuronal loss occurred in the brain. In contrast, the brains of animals given resveratrol had significantly increased concentrations of nitric oxide (NO) and decreased population of hydroxyl radicals. An Indian study demonstrated administration of resveratrol to rats in a model of sporadic AD dementia preserved learning and memory capabilities in passive avoidance paradigms, elevated plus maze and the closed field activity, and lowered the rats' oxidative stress as shown by reduced malondialdehyde (MDA) and glutathione levels, compared to control.[63]

Curcumin, a potent antioxidant extracted from Curcuma longa root (Zingiberaceae, known as turmeric), significantly attenuated 3-NP-induced oxidative stress (lipid peroxidation estimation, reduced glutathione and nitrite activity) in the brains of rats.[64] It also significantly restored deficient succinate dehydrogenase activity, indicating curcumin by its antioxidant activity showed neuroprotection against 3-NP-induced behavioral and biochemical alteration.

In an unpublished study sponsored by Tishcon Corp. and conducted at Little Flower Medical Research Center, Angamaly, India, a special extract of curcumin (as Curcugel™, from Tishcon Corp.) was found to be 8.2-times more bioavailable than normal curcumin. Four human volunteers between ages 20 to 30 were given four capsules (500 mg/ea) of curcumin; all were put on similar diet. Fasting

blood samples were taken and compared to samples taken after volunteers were given Curcu-Gel Softsules containing BCM-95™ (from Orcas International). Researchers concluded bioavailability of curcumin from Curcu-Gel is higher than normal curcumin, on average.

While researchers are still exploring how curcumin works, it appears the botanical extract may help the brain clear amyloid-beta plaque that could otherwise lead to development and progression of AD and other neurological problems, according to researchers from the University of California, Los Angeles.[65] Blood taken from six AD patients and three healthy controls was isolated for macrophages (cells of the immune system that function in the destruction of foreign antigens). The isolated macrophages were exposed to curcumin (as Curcumin C3 Complex, from Sabinsa) in a cell culture for 24 hours, after which time amyloid-beta was introduced. The treated macrophages from the AD patients showed improved ingestion of amyloid-beta compared to those not treated with curcuminoids; and macrophages from the healthy controls, which were shown to be effectively clearing amyloid-beta, showed no changes with curcuminoids treatment. “These initial findings may lead to a new approach in treating AD by enhancing the natural function of the immune system using curcumin, thus increasing the body’s ability to remove plaques that may cause AD and other forms of dementia,” stated UCLA researcher Milan Fiala, M.D. Previous research supports that plaque, specifically from amyloid-beta deposits, could be a contributing factor to the development of AD.

The Macro on Micronutrients

Micronutrient status can affect cognitive function at all ages; deficiencies could influence memory function and might contribute to age-associated cognitive impairment and dementia. For example, **vitamin B6**, comprising three chemically distinct compounds pyridoxal, pyridoxamine, and pyridoxine, is involved in the regulation of mental function and mood.[66] B6 is also an essential **homocystein**e re-methylation cofactor, and deficiency is associated with increase in blood homocysteine levels. Homocysteine, a risk factor for cerebrovascular disease, may also have toxic effects on neurons.

Hyperhomocysteinemia has been suggested as a cause or mechanism in the development AD and other forms of dementia. However, a two-year clinical trial involving 276 older adults found no differences in cognitive function between those given B6 and those receiving a placebo.[67]

Iron status is a significant factor in cognitive performance in women of reproductive age. Severity of anemia primarily affects processing speed, and severity of iron deficiency affects accuracy of cognitive function over a broad range of tasks.[68]

Studies investigating the impact of the B vitamins on cognitive function and homocysteine levels demonstrated dietary intake of folate, B12 and B6 in 1,183 men and women, and found higher intakes of B12 and B6 were positively related to memory function, while higher intakes of folate and B6 were positively associated with better memory function in women.[69]

Studies have suggested a link between **folate** deficiency and dementia onset. A Swiss study investigated the relations of mild cognitive impairment, Alzheimer’s and vascular dementia with serum levels of homocysteine, folate and B12.[70] The human study found hyperhomocysteinemia was significantly associated with dementia and Alzheimer’s, as was low folate status, leading the researchers to suggest folate deficiency may precede the onset of dementia. Similarly, Belgian

researchers found significant negative correlations between levels of serum B12 and folate and degree of cognitive deterioration in 180 patients with Alzheimer's and/or vascular dementia.[71]

As consumers are living longer cognitive decline becomes a bigger societal concern. The right ingredients—from fatty acids to botanicals—can help keep brain degeneration and mood disorders at bay, even as the fine grey lines of time take their course.

References:

1. Lau FC et al. "The beneficial effects of fruit polyphenols on brain aging." *Neurobiol Aging*. 26, Suppl 1:128-32, 2005. www.elsevier.com

2. Rinaldi P et al. "Plasma antioxidants are similarly depleted in mild cognitive impairment and in Alzheimer's disease." *Neurobiol Aging* 24, 7:915-9, 2003. www.elsevier.com

3. Gray SL et al. "Is antioxidant use protective of cognitive function in the community-dwelling elderly?" *Am J Geriatr Pharmacother*. 1, 1:3-10, 2003. www.elsevier.com

4. ibid.

5. Landmark K. "Could intake of vitamins C and E inhibit development of Alzheimer dementia?" *Tidsskr Nor Laegeforen*. 126, 2:159-61, 2006. www.tidsskriftet.no

6. Conte V et al. "Vitamin E reduces amyloidosis and improves cognitive function in Tg2576 mice following repetitive concussive brain injury." *J Neurochem*. 90, 3:758-64, 2004. www.blackwell-synergy.com

7. Nishida, et al. "Deletion of vitamin E enhances phenotype of Alzheimer disease model mouse" *Biochem Biophys Res Commun*. doi:10.1016/j.bbrc.2006.09.083

8. Di Iorio, et al. "Markers of inflammation, vitamin E and peripheral nervous system function: the InCHIANTI study" Neurobiology of Aging. 27,9:1280-8, 2006. doi:10.1016/j.neurobiolaging.2005.07.004

9. Morris MC et al. "Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change." *Am J Clin Nutr.* 81, 2:508-14, 2005. www.ajcn.org

10. Cherubini A et al. "Vitamin E levels, cognitive impairment and dementia in older persons: the InCHIANTI study." *Neurobiol Aging.* 26 7:987-94, 2005. www.elsevier.com

11. Sen CK, et al., "Tocotrienol potently inhibits glutamate-induced pp60(c-src) kinase activation and death of HT4 neuronal cells – Molecular basis of Vitamin E action", *J. Biol. Chem*., 275,17:13049-13055, 2000. www.jbc.org/

12. Sen, Chandan, et al., "Vitamin E sensitive genes in the developing rat fetal brain : a high density oligonucleotide microarray analysis" FEBS Letter, 530:17-23, 2002

13. Khanna, et al. “Characterization of the potent neuroprotective properties of the natural vitamin E α-tocotrienol” *J Neurochem*. 98,5:1474-86, 2006, doi:10.1111/j.1471-4159.2006.04000.x

14. Sen, CK, et al., “Neuroprotective Properties of the Natural Vitamin E Alpha-Tocotrienol”, *Stroke* 36:144 – e 152, 2005. http://stroke.ahajournals.org/

15. Chandan Sen, "Tocotrienol - The Natural Vitamin E to Defend the Nervous System". The *Annals of the New York Academy of Science* 1031; 1-16, 2005. http://www.annalsnyas.org/

16. Young, AJ, et al. “Coenzyme Q10: a review of its promise as a neuroprotectant” *CNS Spectr*. 12,1:62-8, 2007. http://www.cnsspectrums.com/default.aspx

17. Willis R et al. "Clinical implications of the correlation between coenzyme Q10 and vitamin B6 status." *Biofactors*. 9, 2-4:359-63, 1999. http://iospress.metapress.com/

18. Joseph JA, et al “Reversals of Age-Related Declines in Neuronal Signal Transduction, Cognitive, and Motor Behavioral Deficits with Blueberry, Spinach, or Strawberry Dietary Supplementation”, *The Journal of Neuroscience*, 19:8114-8121, 1999. http://www.jneurosci.org/cgi/reprint/19/18/8114.pdf

19. Moreira PI et al. "CoQ10 therapy attenuates amyloid beta-peptide toxicity in brain mitochondria isolated from aged diabetic rats." *Exp Neurol.* 196, 1:112-9, 2005. www.elsevier.com

20. Li G, Zou L, “Neuroprotective effect of Coenzyme Q10 on ischemic hemisphere in aged mice with mutations in the amyloid precursor protein” *Neurobiol Aging*. 28,6,:877-82, 2007. http://linkinghub.elsevier.com/retrieve/pii/S0197-4580(06)00149-7

21. McDonald SR et al. "Concurrent administration of coenzyme Q10 and alpha-tocopherol improves learning in aged mice." *Free Radic Biol Med*. 38, 6:729-36, 2005. www.elsevier.com

22. Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, McEwen JJ, Bickford PC, Reversals of Age-Related Declines in Neuronal Signal Transduction, Cognitive, and Motor Behavioral Deficits with Blueberry, Spinach, or Strawberry Dietary Supplementation, *The Journal of Neuroscience*, 19:8114-8121, 1999. www.jneurosci.org/

23. Bickford P.C., et al, “Antioxidant-rich diets improve cerebellar physiology and motor learning in aged rats” *Brain Res*. 866,1-2:211-7, 2000. DOI:10.1016/S0006-8993(00)02280-0

24. Wang, Y, et al. “Dietary supplementation with blueberries, spinach or spirulina reduces ischemic brain damage.” *Journal of Experimental Neurology*, 193,1: 75-84, 2005. http://www.elsevier.com/wps/find/journaldescription.cws_home/622828/description#description

25. Tso, et al, U.S. Patent No. 5,527,533, 1996. Proprietary Research: Cyanotech Corp.

26. *ibid*.

27. Oryza Oil & Fat Chemical Co. “Natural Antioxidant for Neuro-protection, Vision Enhancement & Skin Rejuvenation.” September 7, 2006.

28. MacLean, C. et al. “Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases” February 2005. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/clinic/tp/o3cogntp.htm

29. Whalley LJ, et al. “Cognitive aging, childhood intelligence, and the use of food supplements: possible involvement of n-3 fatty acids” *AJCN* 80,6:1650-57, 2004. www.ajcn.org

30. Kalmijn S, et al. “Dietary fat intake and the risk of incident dementia in the Rotterdam Study.” *Ann Neurol* 42:776-82, 1997.

31. Barberger-Gateau P, et al. “Fish, meat, and risk of dementia: cohort study” *BMJ*;325:932-3, 2002. www.bmj.com

32. Morris MC, et al. “Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease” *Arch Neurol* 60:940-6, 2003. http://archneur.ama-assn.org/

33. Freund-Levi Y et al “Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial” *Archives of Neurology* 63, 10: 1402- 8, 2006. http://archneur.ama-assn.org/

34. Cao D, et al “Chronic daily administration of ethyl docosahexaenoate protects against gerbil brain ischemic damage through reduction of arachidonic acid liberation and accumulation” *J Nutr Biochem* 18,5:297-304, 2007. doi:10.1016/j.jnutbio.2006.05.005

35. Calon F, et al. “Docosahexaenoic acid protects from dendritic pathology in an Alzheimer’s disease mouse model.” *Neuron* 43:633-645, 2004. www.neuron.org/

36. Lim GP, et al. “A diet rich with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model.” *J Neurosci* 25:3032-3040, 2005. www.jneurosci.org

37. Fioravanti M et al. "Cytidinediphosphocholine CDP-choline for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly." Cochrane Database Syst Rev. 2:CD000269, 2005. www.mrw.interscience.wiley.com

38. Conant R, Schauss AG. “Therapeutic applications of citicoline for stroke and cognitive function in the elderly: A review of the literature” *Altern Med Rev* 9:17-31, 2004. http://www.thorne.com/altmedrev/.fulltext/9/1/17.pdf

39. Babb SM, Appelmans KE, Renshaw PF, et al. “Differently effect of CDP-choline on brain cytosolic choline levels in younger and older subjects as measured by magnetic resonance spectroscopy.” *Psychopharmacology* 127:88-94, 1996. http://www.springerlink.com/content/100390/

40. Thal LJ, Carta A, Clarke WR , et al. “A 1-year multicenter placebo-controlled study of acetyl-L-carnitine in patients with Alzheimer’s disease” *Neurology* 47:705-711, 1996. www.neurology.org/

41. Benton, D. et al. “The influence of phosphatidylserine supplementation on mood and heart rate when faced with an acute stressor” *Nutr Neurosci*.4,3:169-78, 2001. http://www.ingentaconnect.com/content/tandf/gnut

42. Crook, T., J. Tinklenberg, J. Yesavage, et al.; “Effects of phosphatidylserine in age-associated memory impairment”. *Neurology*, 41,5:644-649, 1991. www.neurology.org/

43. Z. Subhan and I. Hindmarch, "Psychopharmacogical Effects of Vinpocetine in Normal Healthy Volunteers", *Eur. J. Clin. Pharmacol*. 28, 567-571, 1985. http://www.springerlink.com/content/100413/

44. Hagiwara, M., Endo, Y., Hidaka, H., "Effects of vinpocetine on cyclic nucleotide metabolism in vascular smooth muscle" *Biochem Pharmacol* 33:453-457, 1984. http://www.elsevier.com/wps/find/journaldescription.cws_home/525454/description?navopenmenu=-2

45. Schmid-Schonbein, H., Grebe, R., Teitel, P., Artmann, G., Eschweiler, H., Schroder, S., "Restoration of microsieve filterability of human red cells after exposure to hyperosmolarity and lactacidosis: Effect of Vinpocetine", *Drug Development Research*, 14, 205-211, 1988. http://www3.interscience.wiley.com/cgibin/jhome/34597?CRETRY=1&SRETRY=0

46. Vohora D et al. "Protection from phenytoin-induced cognitive deficit by Bacopa monniera, a reputed Indian nootropic plant." *J Ethnopharmacol*. 71, 3:383-90, 2000. www.elsevier.com

47. Das A et al. "A comparative study in rodents of standardized extracts of Bacopa monniera and Ginkgo biloba: anticholinesterase and cognitive enhancing activities." *Pharmacol Biochem Behav*. 73, 4:893-900, 2002. www.elsevier.com

48. Stough C et al. "The chronic effects of an extract of Bacopa monniera Brahmi on cognitive function in healthy human subjects." Psychopharmacology Berl. 156, 4:481-4, 2001. www.springerlink.com

49. Singh RH, Singh L. “Studies on the anti-anxiety effect of the medyha rasayana drug, Brahmi (Bacopa monniera Wettst.)-part1” *J Res Ayur Siddha*;1:133-148, 1980.

50. Walesiuk A et al. "Ginkgo biloba normalizes stress- and corticosterone-induced impairment of recall in rats." *Pharmacol Res*. 53, 2:123-8, 2006. www.elsevier.com

51. Walesiuk A et al “Preventive action of Ginkgo biloba in stress- and corticosterone-induced impairment of spatial memory in rats” *Phytomedicine*, May 3, 2007; ePub ahead of print. doi:10.1016/j.phymed.2007.04.012

52. Wang Y et al. "The in vivo synaptic plasticity mechanism of EGb 761-induced enhancement of spatial learning and memory in aged rats." *Br J Pharmacol*. 148, 2:147-53, 2006. www.nature.com/bjp

53. Zhang M et al. "Extract of Ginkgo biloba leaves reverses yohimbine-induced spatial working memory deficit in rats." *Behav Pharmacol*. 16, 8:651-6, 2005. www.behaviouralpharm.com

54. Ho, "Soy isoflavone supplementation and fasting serum glucose and lipid profile among postmenopausal Chinese women: A double-blind, randomized, placebo-controlled trial." *Menopause.* The Journal of The North American Menopause Society, April 10, 2007, ePub Ahead of Print. http://www.menopausejournal.com/pt/re/menopause/abstract.00042192-900000000-99838.htm;jsessionid=GcQC71xVJ3MjJQ9hxG6vhw5WrWcqH50SW1p2dMLTDQT5q2rmbtRw!-1547828331!-949856145!8091!-1

55. Kritz-Silverstein D et al. "Isoflavones and cognitive function in older women" the Soy and Postmenopausal Health In Aging (SOPHIA) Study." *Menopause*. 10, 3:196-202, 2003. www.menopausejournal.com

56. Reay JL et al. "Single doses of Panax ginseng G115 reduce blood glucose levels and improve cognitive performance during sustained mental activity." *J Psychopharmacol*. 19 4:357-65, 2005. http://jop.sagepub.com/

57. ibid.

58. Rudakewich M et al. "Neurotrophic and neuroprotective actions of ginsenosides Rb 1 and Rg 1." *Planta Med*. 67, 6:533-7, 2001. www.thieme-connect.com

59. Kuboyama T et al. "Axon- or dendrite-predominant outgrowth induced by constituents from Ashwagandha." *Neuroreport*. 13, 14:1715-20, 2002. www.lwwonline.com

60. Kuboyama T et al. "Withanoside IV and its active metabolite, sominone, attenuate Abeta 25-35 - induced neurodegeneration." *Eur J Neurosci*. 23, 6:1417-26, 2006. www.blackwell-synergy.com

61. Kuboyama T et al. "Neuritic regeneration and synaptic reconstruction induced by withanolide A." Br J Pharmacol. 144, 7:961-71, 2005. www.nature.com/bjp

62. Lu KT et al. "Neuroprotective effects of resveratrol on cerebral ischemia-induced neuron loss mediated by free radical scavenging and cerebral blood flow elevation." *J Agric Food Chem*. 54, 8:3126-31, 2006. http://pubs.acs.org/journals/jafcau/index.html

63. Sharma M et al. "Chronic treatment with trans resveratrol prevents intracerebroventricular streptozotocin induced cognitive impairment and oxidative stress in rats." *Life Sci.* 71, 21:2489-98, 2002. www.elsevier.com

64. Kumar, P., "Possible neuroprotective mechanisms of curcumin in attenuating 3-nitropropionic acid-induced neurotoxicity" *Exp Clin Pharmacol*. 29,1:19-25, 2007. DOI: 10.1358/mf.2007.29.1.1063492

65. Zhang L, et al. “Curcuminoids enhance amyloid-beta uptake by macrophages of Alzheimer's disease patients” *J Alzheimer’s Dis*. 10, 1:1-7, 2006. http://iospress.metapress.com/link.asp?id=44b34lcyw29fl6v2

66. Malouf R, Grimley Evans J. Vitamin B6 for cognition. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD004393. DOI: 10.1002/14651858.CD004393.

67. McMahon, Jennifer A. et al. “A Controlled Trial of Homocysteine Lowering and Cognitive Performance” *N Engl J Med*. 29,354,26:2764-72, 2006. http://content.nejm.org/cgi/content/abstract/354/26/2764

68. Murray-Kolb LE, Beard JL et al. “Iron treatment normalizes cognitive functioning in young women” *American Journal of Clinical Nutrition*, 85, 3:778-787, 2007.

69. Bryan J, Calvaresi E. "Associations between dietary intake of folate and vitamins B-12 and B-6 and self-reported cognitive function and psychological well-being in Australian men and women in midlife." *J Nutr Health Aging*. 8, 4:226-32, 2004. www.springerpub.com

70. Quadri P et al. "Homocysteine, folate and vitamin B-12 in mild cognitive impairment, Alzheimer disease and vascular dementia." *Am JClin Nutr*. 80, 1:114-22, 2004. www.ajcn.org

71. Engelborghs S et al. "Correlations between cognitive, behavioral and psychological findings and levels of vitamin B12 and folate in patients with dementia." *Int J Geriatr Psychiatry*. 19, 4:365-70, 2004. http://www3.interscience.wiley.com/cgi-bin/jhome/109668552