Special Article

Brain foods - the role of diet in brain performance and health

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The performance of the human brain is based on an interplay between the inherited genotype and external environmental factors, including diet. Food and nutrition, essential in maintenance of brain performance, also aid in prevention and treatment of mental disorders. Both the overall composition of the human diet and specific dietary components have been shown to have an impact on brain function in various experimental models and epidemiological studies. This narrative review provides an overview of the role of diet in 5 key areas of brain function related to mental health and performance, including: (1) brain development, (2) signaling networks and neurotransmitters in the brain, (3) cognition and memory, (4) the balance between protein formation and degradation, and (5) deteriorative effects due to chronic inflammatory processes. Finally, the role of diet in epigenetic regulation of brain physiology is discussed.

INTRODUCTION

The individual genotype together with a number of environmental factors such as nutrition, parental care, social interactions, stress, and diseases, form the basis for the development and functional properties of the brain.[1,2] The relationship between diet and mental health is becoming increasingly recognized,[3] and nutrition has become an important ancillary consideration as a part of the treatment of psychiatric disorders.[4] This has formed the basis for the concept of "brain foods"—foods that can help optimize mental performance.[5]

We do not present here a systematic review of specific outcomes from nutritional intervention studies in relation to brain development and brain health[6–9] but rather a narrative review, in which we discuss the role of diet in 5 key areas of brain neurophysiology that are related to mental health and performance (Figure 1): (1) brain development, outgrowth of neurons and glial cells; (2) signaling networks and neurotransmitters in the brain; (3) cognition and memory, synaptic plasticity; (4) the balance between protein formation, folding, and degradation—the so-called proteostasis; and (5) deteriorative effects of chronic inflammatory processes. Finally, a section is included on the increasing knowledge about the role of the diet in epigenetic regulation of brain function.

Dietary influence on brain health in general

Brain health is not independent of the body's general health status, and all measures that lead to a good and maintained overall physical health will also be beneficial for the brain. Unsurprisingly, adherence to a Western-style diet rich in saturated fat, refined carbohydrates, and high caloric density combined with overeating behavior, which leads to lifestyle diseases, is also a risk factor for impairing brain performance and health.[10]

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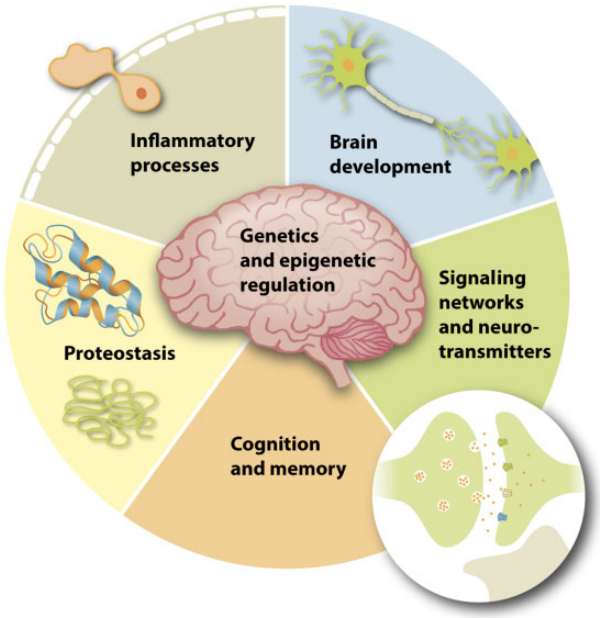

Figure 1 Different aspects of brain structure and function that may be influenced by diet.

Indeed, a direct effect of this type of diet on the human brain has been shown on hippocampus volume,[11] which is important for memory and cognition.

During adult life, brain function is influenced by metabolic disorders such as obesity and type 2 diabetes (T2D).[12,13] Results from a cohort study in Australia, based on demographic data, suggest that, depending on the current trend of mid-life obesity, dementia will increase more than expected in the future.[14] Persons with diabetes have higher risk for Alzheimer disease (AD),[15] and obesity, a risk factor of T2D, is, in itself, related to mood and cognitive disorders.[16] Recent meta-analyses further confirm a relationship between dietary quality and mental health (eg, depression,[17] cognitive function,[7,13,18] and appetite control).[10]

Neuroprotective effects of specific diets: evidence from human studies

The Mediterranean diet, characterized by high intake of monounsaturated fat (eg, olive oil), vegetables, fruits, plant proteins, whole grains, and fish, and relatively low intake of red meat, refined grains, and sweets, has been associated with less cognitive decline in an updated meta-analysis of published, prospective cohort studies that investigated the effects of adherence to the Mediterranean diet on health status, including mild cognitive impairment and stroke.[19] A Mediterranean diet also affects gut microbiota and could exert antidepressant effects via the gut-brain axis.[20]

The DASH (Dietary Approaches to Stop Hypertension) diet is a low-sodium diet rich in fruits, vegetables, and nuts, with low-fat and non-fat dairy, lean meats, fish, poultry, mostly whole-grain cereals, and polyunsaturated fats. A prospective cohort study showed that greater long-term adherence to the DASH diet was associated with better average cognitive function.[21]

Morris et al[22] investigated the role of the Mediterranean plus DASH intervention for neurodegenerative delay (MIND) diet in an intervention study using a diet score that specifically captured dietary components previously suggested to be neuroprotective. This dietary score was positively related to slower decline in global cognition. The difference in decline rates for the top tertile of MIND diet scores vs the lowest was equivalent to being 7.5 years younger.

McEvoy et al[23] evaluated the association among the Mediterranean diet and the MIND diet and cognition in a nationally representative population of older US adults in a cross-sectional study. Cognitive performance was measured using a composite test score of global cognitive function. In this large, representative population of older adults, a high vs a low adherence to the Mediterranean and MIND diets was independently associated with better cognitive function and lower risk of cognitive impairment.

Calorie-restriction diets affect brain function positively in animal models.[24] Few studies have been conducted in humans, but in one of the recent human intervention studies of obese women, intake of a calorie-restricted diet, leading to weight loss, in comparison with a control group with no changes in diet caused improved recognition memory, paralleled by increased gray-matter volume.[25]

Ketogenic diets (very low carbohydrate ketogenic diets) have been popular for short-term weight loss. A recent review of animal and human data supported the beneficial effects of these diets on cognition.[26]

A healthy Nordic diet is characterized by a wide selection of berries, rich in polyphenols, antioxidants, and other bioactive compounds, as well as rye, oats, and barley, often consumed as whole grains rich in dietary fiber. Rapeseed oil is an important source of unsaturated fatty acids in the healthy Nordic diet. This diet is viewed as a potential preventive dietary strategy shown to reduce the risk of cardiovascular disease, T2D, and total mortality.[27] Mannikko et al[28] studied the cross-sectional and longitudinal associations of a healthy Nordic diet with cognitive function. A score indicating high adherence to a healthy Nordic diet at baseline was positively associated with verbal fluency and word-list learning after 4 years of the diet. After excluding individuals with impaired cognition at baseline, the Nordic diet score was also positively associated with the

cognition tests in a follow-up study after 4 years of the Nordic diet.[28]

The Okinawan diet is based on eating habits of the residents of Okinawa, the southernmost prefecture of Japan that has one of the longest life expectancies worldwide. The Okinawan diet is low in fat, particularly saturated fat, high in carbohydrates, and nutrient-dense yet calorie-poor foods, including root vegetables and green leafy vegetables. This is accompanied by a tradition of not overeating. The Okinawan diet is associated with a low risk of age-associated diseases, including dementia.[29]

IMPACT OF THE DIET ON BRAIN DEVELOPMENT

During the early development of the brain, neural and glial cells differentiate from precursor cells and migrate to their final positions.[30] At this stage, the brain overproduces neurons and neuronal connections, and the peak synapse formation is reached between 1 and 2 years of age. Redundant cells and synapses are removed by microglia in a process called synaptic pruning.[31,32] The final stage in fetal brain development is the formation of myelin sheaths, which creates an insulating layer that permits fast signal transduction. Even in adult life, stem cells in the central nervous system remain active,[33] differentiating into neural or glial cells that migrate into the cerebral white or grey matter.[34,35]

During the development of brain structures in prenatal and perinatal phases, it is important that all the necessary energy and nutrients can be absorbed from the diet.[36] The mother's diet during pregnancy already is important for the future brain function of her child.[37] Malnutrition during gestation and early childhood negatively influences development of the brain.[38–40]

The importance of lipids for brain structure and function

Lipids make up half of the human brain by dry weight and are instrumental in vesicle formation, regulation of ion fluxes, creating specialized microenvironments for cellular communication, as well as specific signaling pathways and feedback mechanisms.[41] About 50% of the fatty acids in the brain are polyunsaturated fatty acids (PUFAs), either arachidonic acid (20:4n-6) or docosahexaenoic acid (DHA; 22:6n-3).[42] DHA regulates the function of the glutamatergic synapses related to plasticity and cognitive ability, improves neuronal differentiation,[43,44] and influences gene expression in the brain.[45,46]

Essentially all the arachidonic acid and DHA in the brain are provided by dietary sources, although astrocytes seem to synthesize some of it from n-6 and n-3 precursors.[47] Maternal intake of PUFA influences cell proliferation in the hippocampus of the fetus and newborn infant,[48] and animal studies suggest that brain lipid composition reflects dietary intake and plasma lipid profile.[49] Phosphatidylserine is a polar lipid in neuronal membranes, important for sending and receiving signals in the brain. Supplementation with phosphatidylserine helps prevent cognitive decline and improve memory.[50]

A subgroup of glycosphingolipids, gangliosides, are particularly abundant in the brain.[51] Gangliosides mediate functions such as cell-cell recognition, cell adhesion, motility, and growth.[52] In both human and bovine milk, ganglioside levels are highest in colostrum and decline during transition to mature milk.[53,54] Supplementation with complex milk lipids enhances synaptic plasticity and promotes cognitive development in infants.[55,56] Sialic acid, a component of gangliosides, is in itself an important structural component involved in brain development, learning, and memory.[54,57] Supplementation with human milk oligosaccharides as prebiotics in early infancy may support the establishment of a beneficial gut microbial flora,[58] affecting brain development.[59]

Micronutrients and brain development

Many micronutrients, like vitamins and trace elements, are of essential importance during early brain development.[60] Vitamin B deficiency has been implicated in a number of mental disorders, and the B vitamins B_6, folate (B_9), and B_{12} have been the most widely studied in relation to brain development.[61] Several vitamins and related compounds, including folate, vitamin B_{12}, choline, and glycine betaine, are related to homocysteine concentrations, providing a link to 1-carbon metabolism involved in brain development, including biosynthesis of phospholipids and DNA methylation.[62]

Vitamin D has been called "the neglected neurosteroid" because of the presence of vitamin D–specific receptors in the brain and its effect on brain development.[63] It has a well-known role in the intestinal absorption of calcium,[64] a key actor in synaptic transmission.[65] However, there is a delicate balance, because high intake of calcium and vitamin D is correlated with brain lesions.[66]

Iron is an essential micronutrient involved in neurodevelopment. It is necessary for normal brain development, myelination, and neurotransmission.[67,68]

Zinc plays a key role in neurodevelopmental processes, such as neurogenesis, neuronal migration, synaptic genesis, myelination, and modulation of intra- and intercellular signaling. Severe zinc deficiency causes serious brain structural malformations, but less is

known about if mild to moderate zinc deficiency affects sensorimotor or cognitive development.[69]

Iodine is necessary for the synthesis of thyroid hormones, which are required for normal neuronal migration and myelination of the brain during fetal and early postnatal life; iodine deficiency ("cretinism") leads to irreversible brain damage.[70] Some results indicate that even mild to moderate maternal iodine deficiency causes impairment of cognitive or neurological function in the offspring.[71]

DIETARY EFFECTS ON SIGNALING NETWORKS IN THE BRAIN

There are a number of functional networks in the brain related to different mind states and mood: depression and anxiety; sleep, wakefulness, and arousal; perception of pain, among others. Neuronal signaling is mediated by the release of neurotransmitters (NTs) at synapses between axons and dendrites. There are many types of NTs and other signaling substances in the brain: amino acids (glutamate, γ-aminobutyric acid [GABA], glycine), catecholamines (dopamine, norepinephrine), monoamines (serotonin, acetylcholine), biogenic amines (eg, histamine, tryptamine, tyramine), a number of peptides, purines such as adenosine, and nitric oxide.[72,73] The delicate balance among synthesis, uptake, and regeneration of NTs can easily be disturbed, and NTs that are out of balance constitute one of the main targets when treating neuropsychiatric disorders.

Many dietary components can affect the amount and effect of NTs.[74] The amino acid tryptophan is the precursor of serotonin, and dietary supply of tryptophan can influence serotonin levels in the brain.[75] The amino acid tyrosine is the precursor of the NTs dopamine and norepinephrine. Tyrosine supplementation seems to enhance cognitive performance, particularly in stressful situations.[76] The biogenic amines histamine and tyramine, present in stored or fermented foods, are active NTs in the brain per se,[77] binding to specific receptors.[78]

Diet and depression

Depressive disorders are the most common mental health problem. They incur considerable burden not only for individuals but also for the society. Subclinical symptoms of depression and anxiety are also highly prevalent across the general population among those without clinically diagnosed mental disorders. Therefore, new adjunctive methods to address symptoms of depression and anxiety across the population are welcome. Emerging evidence suggests diet may influence the onset of mood disorders. In a recent meta-analysis of 16 eligible randomized controlled trials, including calorie-restricted diets with increased proportions of fruits, vegetables, fatty fish, whole-grain cereals, nuts, and seeds, dietary interventions significantly reduced depressive symptoms.[79] The MooDFOOD prevention trial concluded there is an adverse effect of sugar intake from sweet foods and beverages on long-term psychological health.[80–82] The SUN cohort study, investigating the association between intake of vitamins and trace elements and mental health, found that inadequacy in any 4 or more micronutrients could increase the risk of development of depression.[83] Results from the project MyNewGut suggested patients with depression should adhere to a plant-based diet with high levels of polyphenols, grains and fibers, and fish with PUFAs,[20] based on findings that individuals who consume a Mediterranean diet have lower rates of depression.

It has also been reported that adequate n-3 PUFA intake affects mood disorders, with improvements in uni- and bipolar depression.[84] There is an inverse relationship between n-3 PUFA concentration in the plasma and risk of psychological distress.[85,86] In terms of differences in national dietary practices, low intake of fish and seafood has been associated with a higher national prevalence of depression and schizophrenia.[87] In older people, low levels of vitamin B_6 and B_{12} as well as higher homocysteine levels have been reported to be associated with symptoms of depression.[88] Much attention has also been devoted to folate depletion and depression.[89] Magnesium is essential for depressing hyperexcitatory activity caused by glutamate, which plays a key modulatory role in response to fear, anxiety, and panic.[90]

Several substances in the diet have direct and indirect effects on pathways linked to depression. For instance, β-carboline alkaloids that are synthesized endogenously in the body, functioning as the brain's own benzodiazepine analogs, are also reported to be widely distributed in many plant species.[91] Coffee is a rich source of β-carbolines, which are formed during roasting.[92]

Vignes et al[93] showed that epigallocatechin gallate (EGCG) from green tea can induce anxiolytic activity in a dose-dependent manner.[94] L-Theanine (γ-glutamylethylamide), an amino acid also found in green tea, is reported to have protective effects against psychiatric disorders such as anxiety, panic, and depression[95] and is used as a therapeutic supplement for patients diagnosed with schizophrenia.[96,97] Grapes contain the stilbenoid resveratrol that inhibits norepinephrine and serotonin reuptake, thereby decreasing anxiety and depressive behaviors.[88,98]

Sleep and wakefulness

Because the brain is active at all times of the day and night, sleep is a vital physiological process with restorative functions. In combination with the excitatory NT glutamate, GABA modulates the inhibitory/excitatory balance necessary for proper brain function.[99]

Melatonin (*N*-acetyl-5-methoxytryptamine) is a compound that has many important functions in the body[100] and also plays an important role in the sleep-wake cycle.[101] Melatonin levels increase at nightfall, causing drowsiness and a lowering of body temperature. Melatonin itself and its precursor, tryptophan, are present in a number of foods, for example, in animal sources like meat, fish, eggs, and milk, and plant foods like cereals, vegetables, and fruit; therefore, the diet may influence melatonin levels in the brain.[102,103]

Some vitamins can play a role in inducing sleep and relaxation. Vitamin B_{12} may have a positive effect on sleep quality, and vitamin B_3 (niacin) allows more tryptophan to be processed to serotonin and melatonin, whereas vitamin B_6 is involved in the production of serotonin from tryptophan.[104] Vitamin D influences the expression of genes important for the regulation of the circadian rhythm.[105] Valerian (*Valeriana officinalis*) is the world's top-selling herbal supplement for insomnia and its sedative effects have been recognized since the 18th century.[106–109] Chamomile (*Matricaria chamomilla*) is frequently used to reduce anxiety and treat sleep problems; its sedative effect is due to a benzodiazepine-like action on $GABA_A$ receptors in the brain.[110] Passionflower (*Passiflora incarnata*) and lemon balm (*Melissa officinalis*) are also used as anxiolytic and sleep-inducing herbal remedies.[111–113]

The neuropeptides orexin A and B produced in the feeding center of the hypothalamus are important for the maintenance of wakefulness, demonstrated by the fact that the sleep disorder narcolepsy is caused by orexin deficiency.[114] Activation of orexin signaling might be related to the amino acid content in diet.[115] Strong evidence suggests the biogenic amine histamine, which is frequently found in many types of food products, also has a pivotal role in the regulation of sleep-wakefulness.[116]

Adenosine is a breakdown product of energy-rich compounds such as adenosine triphosphate and adenosine diphosphate and therefore signals energy depletion via its receptors. It is produced in the brain during the day, with the increasing concentration inhibiting acetylcholine signaling, creating drowsiness. Caffeine and theophylline are antagonists to adenosine receptors.[117] Caffeine also increases focused attention and enhances activity via an indirect effect on dopamine.[118–120] However, there is evidence that caffeine can negatively affect blood flow and oxygen supply in the brain through vasoconstriction.[121]

Intake of dietary inhibitors of the enzyme catechol-*O*-methyl transferase, a catabolic regulator of NTs such as dopamine and norepinephrine, has been found to lead to increased alertness.[122] One example is mangiferin, present in mango (*Mangifera indica*).[123]

Pain

Pain is caused by harmful stimuli such as tissue damage or inflammation. These signals are balanced by endocannabinoid and endorphin analgesic control.[124] Other analgesic agonists, such as palmitoylethanolamide and oleoylethanolamide,[125] are synthesized endogenously in the body but can also be supplied by dietary sources (eg, egg yolk).[126] Caffeine is an antagonist of the glycine receptor, which explains some of its pain-relieving effect.[127] Taurine, an β-amino acid containing a sulphonic group, is reported to be present in most mammals and exerts analgesic effects via the GABA and glycine receptor systems.[128] Because endogenous synthesis of taurine decreases with age, it is mostly supplied via dietary sources such as seafood and meat, and stored in the liver. Chocolate contains phenylethylamine, a molecule that resembles amphetamine and affects dopamine, norepinephrine, and serotonin reuptake, resulting in pain-relieving effects.[129]

Both arachidonic acid and DHA are precursors of endogenous ligands to the cannabinoid receptors, so-called endocannabinoids.[130] From arachidonic acid 2 endocannabinoids are formed: arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol. Besides pain control, there is also evidence for the role of endocannabinoids in a variety of physiological processes, such as brain development, motor function, memory, and cognition.[131] DHA is a precursor of a similar derivative, *N*-docosahexaenoyl ethanolamine, called synaptamide, which has many interesting functions in the brain, including promoting neurogenesis.[132]

A notable commercial trend in food-derived supplements today is the increased market for products based on hemp (*Cannabis sativa*), "CBD" products rich in cannabidiol, which are claimed to be effective against pain, inflammation, and neurodegenerative disorders.[133,134] However, at present, their regulatory status in various markets remains uncertain.

The gut-brain axis

Highly coordinated interactions between the brain and the peripheral metabolic organs are necessary for the maintenance of energy and glucose homeostasis in the

body. This is enabled by the brain monitoring of food intake, energy expenditure, insulin secretion, hepatic glucose synthesis, and glucose and fatty acid metabolism.[135] Signals in response to hunger and satiety can also regulate neurogenesis by modulating the activity in the hypothalamus.[136]

There is increasing evidence for critical interactions between intestinal microbiota, host genetics, environmental influence, and mental health or psychiatric disorders later in life.[137–140] The establishment of the gut-brain axis via the gut microbiota during early development is of great importance, especially in the preterm infant.[38]

In the gut-brain axis, the microbiota can connect to the brain via direct vagus nerve signaling[141] or by receptors specific for intestinal and microbial metabolites.[142] This interplay between the gut microbiome and the brain has been shown to explain the connection among mental stress, immune system activity, and gastrointestinal disorders such as irritable bowel syndrome and inflammatory bowel disease.[143] The gut microbiota has a direct effect on the availability and metabolism of many NTs.[141,144] There is also a link between the microbiome and neurological diseases, such as depression,[145] schizophrenia, and bipolar disorders.[146]

The gut microbiota is influenced, among several factors, by the consumption of dietary fiber,[147] and dietary fibers are of interest for brain health for several reasons.[148] Khan et al[149] found a positive correlation between specific dietary fiber intake and cognitive performance in children. Metabolism of fermentable dietary fiber allows the formation of the short-chain fatty acid butyrate, which has health-promoting effects on the brain, either via epigenetic modifications in the brain or through binding to specific receptors in the gut.[150,151] A recent study demonstrated that supplementation with partially hydrolyzed guar gum to diets of autism spectrum disorders children helped improve gut function and attenuate the level of serum inflammation cytokines and behavioral irritability.[152]

In connection with diet, specific interactions have been found between peripheral metabolic signals and centrally released regulators of food intake and arousal, which are linked to mood disorders.[153] Important players are neuropeptides from the gastrointestinal tract that act on the brain, like cholecystokinin, ghrelin, peptide YY, glucagon-like peptides, and gastric inhibitory polypeptide.[154] The orexigenic peptide galanin can influence intake of fat and alcohol.[155] Release of peptide hormones is altered in conditions like obesity and T2D, affecting brain activity and mood via the gut-brain axis.[156]

Hydrolysis of dietary proteins can also produce bioactive peptides that can have signaling functions or interfere with other signal transduction pathways. Dipeptidyl-peptidase 4 inhibitors will influence the amount of glucagon-like peptide-1 and gastric inhibitory polypeptide. If this enzyme can be deactivated, the satiety effect of glucagon-like peptide-1 will be prolonged.[157] Proteins from amaranth seed (*Amaranthus hypochondriacus*), cowpea bean (*Vigna unguiculata*), pea, soy, hemp protein, cuttlefish, rice, yogurt, macroalga (*Palmaria palmata*), and tuna juice (*Thunnus tonggol*) have all been shown to give rise to bioactive peptides with dipeptidyl-peptidase 4 inhibition activity during digestion.[158,159] Peptides from soy milk binding to cholecystokinin-A receptors may induce satiety.[160] Agonists and antagonists of peripheral μ-opioid receptors (eg, *β*-caseomorphins) are formed from bovine milk proteins.[161,162]

The taste receptors in the gut, similar to the ones found in the oral cavity, and sensitive to food components like monosaccharides, amino acids, and substances causing bitter taste, are important for signaling from the gut to the brain.[142] Recently, Kaelberer et al[163] discovered that enteroendocrine cells in the gut behave like presynaptic cells, secreting glutamate. This neuronal signaling can fire action potentials that ascend to the brain in milliseconds, whereas endocrine effects via peptide hormones will require several minutes before having an impact.

DIETARY INFLUENCE ON COGNITION AND MEMORY

Cognition and memory are central processes in brain performance; they depend on neuronal networks and processes still not fully understood. An important concept for brain function is *synaptic plasticity*, which means that specific experiences can be transformed into memories by long-term potentiation and that memories can be lost due to long-term depression of synaptic activity. The basic mechanisms underlying plasticity include neurogenesis, activity-dependent refinement of synaptic strength, and pruning of synapses. New synapses can be formed depending on the pattern of incoming stimuli. This is connected to the formation of mini-networks of neurons connected to single memories, so-called engrams.[164,165] Changes in plasticity are closely linked to changes in cognitive performance.[166] There is evidence that neural plasticity is stimulated by learning and novelty and enhanced by dietary manipulations and aerobic exercise.[167]

The hippocampus is a region of the brain known to regulate learning, memory, and mood, and capable of continuous generation of new neurons.[168,169] This is essential for cognitive and emotional regulation; its decline leads to severe impairment of learning abilities as

well as increased depressive and anxiety-related behaviors.[170]

Glutamate, the main excitatory transmitter in neuronal cognition networks, acts on Ca^{2+} channel–coupled *N*-methyl-D-aspartate receptors, which are negatively regulated by Mg^{2+} and, therefore, reduce neuronal hyperexcitability, and supplementation of Mg^{2+} has been shown to improve learning and memory.[171] A third divalent metal ion, Zn^{2+}, is involved in glutamate release by binding to *N*-methyl-D-aspartate receptors.[172] $Zn^{2+}$is therefore essential for proper brain function, and the hippocampus and some other brain regions are highly enriched in Zn^{2+} ions.[173]

The advanced signaling functions in the brain require a highly controlled and protected microenvironment, which is provided by the blood-brain barrier.[174,175] In the pathology of the ageing brain, one can find indications of a break-down in the blood-brain barrier, indicated by, for example, traces of blood-derived albumin in the cerebrospinal fluid. Sustaining blood-brain barrier integrity and impermeability with nutritional strategies, therefore, may contribute to the maintenance of cognitive function.[176]

The brain depends on the glucose supply as its main source of energy.[177] Factors that affect glucose uptake can affect both short- and long-term cognitive function. There is a link among glucose metabolism, mitochondria function, and energy supply on the one hand and long-term risk of dementia on the other.

Diet and lifestyle play an important role in halting the progression of neurodegenerative diseases and impaired cognitive function, through the enhancement of structural and functional plasticity in the hippocampus, increased expression of neurotrophic factors, maintenance of synaptic function, and adult neurogenesis.[169] Dietary interventions have emerged as potential inducers of brain plasticity (eg, calorie restriction, intermittent fasting).[178,179] There is a long-term positive effect on cerebral blood flow in response to lifestyle interventions with a calorie-restricted diet, weight loss, and increased physical activity.[180] To provide the brain with all components necessary to support the synthesis of new synapses and maintenance of existing neuronal connections, thereby possibly reducing the consequences of AD, specially designed multicomponent diets have been proposed (eg, Souvenaid [Fortasyn Connect]).[181,182] This diet contains DHA, eicosapentaenoic acid, uridine monophosphate, choline, folic acid, and vitamins B_6, B_{12}, C, and E, in addition to elements such as selenium and phospholipids.[183] The therapeutic potential of specially designed diets containing precursors of membrane phospholipids and prebiotic fibers has also been demonstrated in a mouse model of Parkinson disease (PD).[184]

Although the evidence is inconclusive, it has been suggested that n-3 PUFA supplementation can slow cognitive decline among older people without dementia,[185,186] play a role in preventing the onset of age-related dementia,[187] and the deposition of amyloids.[188] A longitudinal study of older adults over 4 years measured plasma levels of eicosapentaenoic acid and DHA, and found less cognitive decline related to high PUFA levels in plasma.[189] Using magnetic resonance imaging techniques, beneficial results have been found in a 26-week randomized controlled trial .[190] A meta-analysis conducted by the Cochrane Library concluded there is insufficient evidence that n-3 PUFAs affect cognitive decline.[191] Because n-3 PUFAs have been associated with fish consumption, this suggests there might be a link with consumption of whole fish, and that other components in fish may be beneficial. The fish protein β-parvalbumin inhibits α-synuclein amyloid formation and may thus protect against PD.[192]

Other lipid compounds of nutritional interest are medium-chain triglycerides, which are quickly converted in the body into ketones, and can be used by the brain as an extra energy source.[193] Studies in rodents bred to develop AD showed cognitive benefits of the rodents receiving medium-chain triglycerides. There have been a few studies performed of medium-chain triglyceride supplementation effects on cognitive capacity in humans.[194]

Among vitamins, the metabolite of vitamin A, retinoic acid, is a potent signaling molecule in the brain that affects neurogenesis, neuronal survival, and synaptic plasticity.[195] Folic acid supplements, with or without other B vitamins, have not yet been found to improve cognitive function or prevent dementia or AD, but more research is needed.[196] A meta-analysis focusing on intake of vitamin B_{12} and other vitamin B components for homocysteine lowering showed no effect on cognitive ability in ageing.[197] However, supplementation with B vitamins including folate and B_{12} reduced diminishing of brain volume over 2 years in elderly individuals with hyperhomocysteinemia, which is associated with dementia.[198]

Some studies have linked low levels of vitamin D to memory deficits and dementia.[199] A meta-analysis showed that lower serum vitamin D concentrations are associated with poorer cognitive function and a higher risk of AD.[200] High intake of vitamin E has been associated with a lower risk of dementia,[201] and circulating concentrations of vitamin E are influenced by apolipoprotein E genotype, which is associated with AD risk,[202] but the cause-and-effect mechanism of this relation is unclear. It is uncertain whether there are possible benefits of vitamin E supplementation for patients with AD who already have adequate levels of the vitamin.[203]

Several phenolic compounds of plant origin have been found to affect the cognitive functions of the brain in model systems and animal studies[204–208] and to have a protective effect against cognitive decline.[209,210] The Invecchiare in Chianti epidemiologic study showed that high concentrations of polyphenols were associated with lower risk of cognitive decline in an older population.[211]Resveratrol-treated animals exhibited increased neurogenesis and microvasculature in the hippocampus.[212] Dietary supplementation with a specific grape-derived polyphenolic preparation significantly improved cognitive function in a mouse model of AD.[213] In a systematic review of human studies, moderate intake of coffee or caffeine-rich beverages reduced cognitive decline.[214]

Another case is EGCG from green tea, which has been reported to improve cognitive performance.[215] The effect of lemon balm on cognitive ability is explained by its content of substances with cholinergic receptor–binding properties.[216] Dietary carotenoids, such as lutein and zeaxanthin, are important not only for eye health and vision but also for cognitive abilities.[217] Ursolic acid is a triterpenoid found in apple peels and rosemary (*Rosmarinus officinalis*), and has been reported to have effects on cognition and intelligence.[218,219] Bryostatin, a macrolide lactone in the marine bryozoan *Bugula neritina*, can prevent synaptic loss and facilitate synaptic maturation in patients with AD.[220]

Evidence suggests that blueberries (*Vaccinium myrtillus*), rich in phenolic substances such as flavanols and anthocyanidins, have beneficial effects on spatial working memory and cognition in rats.[221–224] Blueberries are also reported to be beneficial for dopaminergic regeneration in animal models of PD.[225,226]

THE ROLE OF DIET IN THE BALANCE BETWEEN PROTEIN FORMATION AND DEGRADATION

The balance of protein synthesis, folding, and degradation—called proteostasis—is an essential part of nerve cell function that might be affected by ageing.[227] The so-called unfolded protein response caused by the formation of misfolded proteins and their polymers in neuronal cells is associated with several neurodegenerative diseases,[228] such as AD, PD, Huntington disease, Pick's disease, as well as Lewy body and frontotemporal dementia.[229] Proteins similar to the amyloid-β precursor, which normally have important physiological roles (eg, in binding to GABA receptors),[230] form oligomers and polymers with deleterious effects on brain function. Normally, dysfunctional proteins are safely degraded via either the ubiquitin/proteasome system or the lysosomal autophagy pathway.[231,232] The delivery of debris to lysosomal degradation is often mediated by chaperones,[233] many of which exhibit aberrant expression in the brain of patients with mental disorders.[234,235]

It is now clear that the capacity of cells to maintain proteostasis undergoes a decline during aging, rendering the organism susceptible to degenerative pathologies.[236] Already, oligomers and small aggregates of misfolded proteins may be toxic to the nerve cells; therefore, any substance that can inhibit the formation of oligomers or their interaction with cellular membranes will possibly retard their degenerative effects on nerve cells, and green tea EGCG is reported to inhibit the toxicity of α-synuclein oligomers.[237]

Proteostasis is closely related to energy supply and proper mitochondrial function. The insulin-like growth factor-1 plays an essential role in energy metabolism in the brain. The metabolic capacity of the mitochondria depends on the insulin-like growth factor-1 (IGF-1) signaling pathway.[238] The degradative product of IGF-1, cyclic glycine-proline, is a key factor in the brain that normalizes IGF-1 signaling, essential for cognitive function.[239] Several clinical trials in which patients with PD received supplementation of black currant anthocyanins extract have demonstrated increased levels of cyclic glycine-proline.[240]

The protein aggregates affecting neuronal function in the brain may also be of peripheral origin.[241]Diabetes-related increase in advanced glycation end-products and their receptors can actively increase the transport of $\beta-$amyloid oligomers of peripheral origin into the brain.[242] Another important mechanism in AD is the early sign of restriction in cerebral blood flow, caused by the effect of amyloid β oligomers on pericytes surrounding the capillaries in the brain.[243]

When searching for key molecular hubs for the cellular regulation of the processes leading to cognitive decline and dementia, using systems biology, the AMP-activated kinase signaling network turned out to be a core process, coupled to changes in autophagy and proteostasis.[244] AMPK plays a key role in energy sensing in the cell, including brain cells, and AMPK activators including dietary components are used to decrease the risk of T2D and cardiovascular disease. AMPK dysfunction and abnormal activation have been connected to the progression of several protein aggregate–associated neurodegenerative diseases (eg, AD, PD, Huntington disease)[245] and could be a possible target for dietary strategies to regulate early stages of cognitive decline.[246,247]

DIETARY PROTECTION AGAINST NEUROINFLAMMATORY PROCESSES

Acute neuroinflammation is a protective process that isolates the injured brain tissue from the uninjured areas, destroys injured cells, and rebuilds the

extracellular matrix. Chronic neuroinflammation, where inflammatory processes are active over many years, causes damage to the brain tissue.[248] It is closely associated with the activation of microglia and astrocytes, which causes inflammatory responses[249,250] such as the secretion of prostaglandins and other mediators of pro-inflammatory as well as protective signals.[251] Microglial cells are normally relatively quiescent but can respond to signals from the peripheral immune system and induce neuroinflammation. During aging, microglia tend to transit into a more pro-inflammatory state, producing excessive levels of inflammatory cytokines that lead to cognitive dysfunction.[252]

Prolonged exposure to stress often leads to the exacerbation of inflammatory processes, increased risk of age-related brain disorders, and cognitive deficits.[253,254] An effect of stress is the permanent activation of the hypothalamo-pituitary-adrenal axis, resulting in increased cortisol levels related to depression.[255–257]

Oxidative stress is an important factor in age-related tissue damage in the brain. Large amounts of iron are sequestered in melanin granules in the dopaminergic neurons of the substantia nigra and the noradrenergic neurons of the locus coeruleus.[258] Increased iron accumulation can affect the ageing of the brain via oxidative stress.[259]

Specific types of monosaccharides in the diet influence brain development or function in rodent models: High fructose consumption in rats led to decreased neurogenesis[260] and neuronal loss in the nucleus tractus solitarius, the main region in the brain for cardiovascular regulation.[261] Moreover, galactose can cause increased oxidative stress and impaired neurogenesis in mice,[262] promote formation of free radicals, and decrease the expression of antioxidative enzymes, inducing ageing and memory loss,[263,264] Galactose exposure, therefore, is used as a model of oxidative damage in the brain.[265] Because monosaccharides have an overall impact on metabolism, it can be hard to identify direct effects on neurodevelopment and function, especially when the proportion of monosaccharides in the experiment is very different to that in normal human diet.

Glutathione is the main endogenous, free radical scavenger in the body and levels decrease during oxidative stress.[266] The highest concentration of vitamin C in the body is found in the brain, which is the most difficult organ to deplete of ascorbate.[267] Heme oxygenase-1 (HO-1), an important enzyme for antioxidant defence in brain tissue, cleaves heme to remove pro-oxidative iron, modulates inflammation, and contributes to angiogenesis.[268] Other important agents for intracellular protection against oxidative stress are the peroxiredoxins, which may be affected by diet via the NF-κB pathway.[269]

A number of compounds normally present in foods have anti-inflammatory and neuroprotective properties. The glutathione content in the brain is positively related to intake of dairy products in older people.[270] Dietary components such as α-lipoic acid and *N*-acetylcysteine reverse memory impairment in animal models[271] and successfully raise plasma glutathione levels in patients with schizophrenia.[272,273] Green tea increases glutathione levels while reducing symptoms of depression,[274] suggesting that improving endogenous antioxidant systems may be neuroprotective.

Flavonoid compounds in fruits and vegetables, as well as n-3 PUFAs from seafood, might restore the population of microglial cells in the senescent brain to a more quiescent state.[224,275,276] The phenolic substance curcumin, present in turmeric (*Curcuma longa*), may protect cortical neurons against apoptotic cell death induced by β-amyloid peptides[277,278] and alleviate symptoms of depression by enhancing neurogenesis in the hippocampus and frontal cortex.[204] It also induces HO-1 expression.[279,280] A recent double-blind, placebo-controlled study of curcumin supplementation showed significant benefits for memory and attention in participants with mild memory complaints.[281] However, although many in vitro studies suggest potential benefits of some phenolic compounds, they might have poor gastrointestinal bioavailability.[282] This suggests bioavailability is essential in the formulation.[205,283]

Caffeic acid phenethyl ester, found in the bark of conifer trees and bee honey propolis,[284] is a potent inducer of HO-1 in neurons and astrocytes.[285] Ethyl ferulate from plants of the Solanaceae can induce HO-1 in rat astrocytes and hippocampal neurons[286] as well as provide protection against the toxicity induced by amyloid peptides.[287]

EGCG in green tea is reported to exert neuroprotective effects and to alleviate symptoms of stress and depression,[204,288] partly due to increased expression of HO-1.[289] It is believed that sulforaphane, present in cruciferous vegetables, may activate genes in astrocytes and neurons protective against inflammation.[290]

Arctic root (*Rhodiola rosea*) contains components such as salidroside, rosavins, and *p*-tyrosol, reported to suppress oxidative stress, neuroinflammation, and excitotoxicity.[291] Flavonoids from citrus fruits (ie, nobiletin, tangeretin) are neuroprotective in AD and PD.[292]

Johnson et al[293] discovered that substance P has a proinflammatory effect, leading to cytokine release. Therefore, antagonists of substance P receptors could have a potential for alleviating chronic inflammatory conditions in the brain.[294] Presently, only a few natural compounds that interact with these receptors have been identified (eg, from herbs like chamomile).[295]

CONNECTION BETWEEN DIET AND EPIGENETIC PROGRAMMING

The mental health status of each person is related to individual variability in numerous protein-coding and noncoding regions of the genome.[296] Throughout life, epigenetic modulations influence gene expression in response to endogenous and exogenous regulators. Recently published data on gene expression in relation to brain development and neuropsychiatric disorders provide an extensive publicly available genomic resource.[151,297] Approximately 1.5% of the human genome is made up of coding DNA and 98.5% of noncoding DNA. Most of the genetic variation resides in the noncoding regions, and mutations in these regions are decisive for brain function and disorders.[298] For instance, the serotonergic system is influenced by early nutrition and stress, causing epigenetic modifications that affect expression and are linked to bipolar disorders and depression later in life.[296,299]

Many of the connections between diet and brain health are mediated by epigenetic mechanisms, such as methylation of nucleotides, acetylation, phosphorylation, and other posttranslational modifications of histones, transcription of microRNA from noncoding DNA, and changes in the topological arrangement of three-dimensional structures of DNA.[300,301] The emerging role of noncoding DNA sequences as key regulators of transcription, epigenetic processes, and gene silencing will create a new basis for understanding of dietary influence on the brain. The major NTs dopamine and serotonine themselves can modify histone H3 by monoaminylation and thereby affect brain regions epigenetically and influence behaviour.[302,303]

The mother's dietary situation during the first months of pregnancy and early nutrition of the newborn infant can influence epigenetic programming in both irreversible and reversible ways.[60,304] A deficiency of essential nutrients or general famine in a population might even lead to transgenerational effects. Later in life, a high-fat diet and obesity can affect epigenetic programming. During aging, there is a general increasing risk of aberrant epigenetic modifications, which is a possible explanation for cognitive and functional decline in the brain.[305,306]

Several additional direct connections between nutrition and epigenetics have been identified.[307] For instance, methionine, folic acid, vitamins B_6 and B_{12}, choline, and glycine betaine are all important for the one-carbon metabolism that can affect DNA methylation. This includes the methyl donor *S*-adenosyl methionine, which is available as a food supplement.[308,309] Biotin is a substrate for histone biotinylation, niacin is involved in histone adenosine diphosphate-ribosylation and deacetylation, and panthotenic acid is a part of coenzyme A involved in the transfer of acetyl groups in acetylation. Genistein from soy and tea catechins affect DNA demethylation and histone modification, whereas resveratrol (in red wine), sulforaphane (in broccoli), butyrate, diallyl sulfide (in garlic) and curcumin (in turmeric) all affect histone acetylation; and retinoic acid affects microRNA transcription.[310] The olive tree (*Olea europaea*) synthesizes substances that have neuroprotective effects, partly via epigenetic modifications (eg, oleuropein, tyrosol, hydroxytyrosol).[311,312]

A challenge for nutrition science will be to analyze how dietary components specifically interact with the most important regulatory elements on an individual level, taking into consideration both genotype and phenotype affected by environmental factors such as diet and gut microbiota and partly mediated via epigenetic modifications. This will create a new level of interactive knowledge in the field of "personalized neuronutrition," made possible by the rapidly expanding data sources from genome-wide studies related to brain development, function, and health.

CONCLUSIONS AND PERSPECTIVES: A NOTE OF CAUTION AS WELL AS OPTIMISM

Looking at the overall connection between nutrition and brain development and function, the simple rule is that "what is good for your heart, is good for your brain." Thus, an overall healthy diet from both a cardiovascular and weight management point of view, considering the risk of insulin resistence, will also be good for the brain.[8]

Early nutrition—the diet of the pregnant mother and the nutritional status of the newborn baby and the young infant—influences the development of the brain, together with other environmental factors and long-term epigenetic mechanisms. From the perspective of the important balance between the formation of synapses and neurons and the necessary pruning of synapses during childhood and adolescence, the question remains about whether one-sided promotion of neuronal growth will be beneficial for brain performance or if it will lead to unintended negative consequences.

Signaling networks in the brain, connected to mood and behavior, like depression, sleep and wakefulness, pain, and so on, are influenced by specific NTs and networks between specific centers in the brain, and can be influenced by dietary components either affecting the amounts and effect of the active NTs or interfering with relevant receptors.

An important factor is the gut-brain axis, the connection between the vagus nerve and receptors in the gut epithelium—peptide hormones secreted in the gut,

with substances present in the food or formed during digestion, cause signals or be transported to the brain. This includes the gut microbial flora and its metabolites.

Cognition and memory depend on energy supply; therefore, the cardiovascular status of the brain will be an important factor, as well as the proper function of mitochondria. Intimidation of glucose and oxygen transport to the brain and mitochondrial energy production will have consequences for synaptic plasticity, important for cognition and memory. The same is valid for the ability of cells to cope with the production of unfolded or misfolded proteins and their removal via proteasomes or autophagy. There is increasing evidence that some protein aggregates influencing neuronal function are imported from peripheral sources.

In general, chronic inflammation is deleterious to the brain as to other parts of the body; therefore, many dietary components with anti-inflammatory effects have been of interest in designing neuroprotective diets. Finally, there is an increasing knowledge of the more long-term epigenetic effects of environment and diet on brain function.

To summarize, the results of several studies support the concept of "brain food" and the notion that diet has an important effect on aspects of brain function, but conclusive evidence is still lacking in many cases. Indeed, alertness and mood can be modulated by the daily diet. However, it is also clear that people with suboptimal diets can still function normally, even at a high level of cognitive demand, although severe malnutrition remains a major impediment to neurocognitive development. Improving nutrient status can enhance learning outcomes, especially when access to nutritious foods is limited.

There are many suggestions on how diet and nutrition status specifically interact with mental health, cognitive development, and decline. Several case studies have reported that individuals who may be genetically predisposed to nutrient deficiencies can benefit from dietary changes to help address mental disorders. From this perspective, the concept of personalized nutrition may be useful for identifying people who may benefit from foods that support brain function and overall improved nutrient status. If such methods can help detect, in the initial stages, people who are at risk for development of, for example, dementia spectrum diseases, there will be a very strong case for greater emphasis on diet and dietary support to prevent cognitive decline due to age. Therefore, it is important to combine a greater knowledge of the influence of diet on the basic processes and mechanisms of brain development, function, and age-related decline, with an overall nutritional approach, as well as more efficient use of the specific effects of individual dietary components.

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REFERENCES

1. Gandal MJ, Haney JR, Parikshak NN, et al. Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. *Science*. 2018;359:693–697.
2. Bedrosian TA, Quayle C, Novaresi N, et al. Early life experience drives structural variation of neural genomes in mice. *Science*. 2018;359:1395–1399.
3. Spencer SJ, Korosi A, Laye S, et al. Food for thought: how nutrition impacts cognition and emotion. *NPJ Sci Food*. 2017;1:7.
4. Sarris J, Logan AC, Akbaraly TN, et al. Nutritional medicine as mainstream in psychiatry. *Lancet Psychiatry*. 2015;2:271–274.
5. Lanni C, Lenzken SC, Pascale A, et al. Cognition enhancers between treating and doping the mind. *Pharmacol Res*. 2008;57:196–213.
6. Vauzour D, Camprubi-Robles M, Miquel-Kergoat S, et al. Nutrition for the ageing brain: towards evidence for an optimal diet. *Ageing Res Rev*. 2017;35:222–240.
7. Jacka FN. Nutritional psychiatry: where to next? *EBioMedicine*. 2017;17:24–29.
8. Global Council on Brain Health. Brain-Food GCBH recommendations on nourishing your brain health. 2018. Available at: http://www.GlobalCouncilOnBrainHealth.org. Accessed March 2020.
9. Global Council on Brain Health. The real deal on brain health supplements: GCBH recommendations on vitamins, minerals and other dietary supplements. 2019. Available at: http://www.GlobalCouncilOnBrainHealth.org. Accessed March 2020.
10. Stevenson RJ, Francis HM, Attuquayefio T, et al. Hippocampal-dependent appetitive control is impaired by experimental exposure to a Western-style diet. *R Soc Open Sci*. 2020;7:191338.
11. Jacka FN, Cherbuin N, Anstey KJ, et al. Western diet is associated with a smaller hippocampus: a longitudinal investigation. *BMC Med*. 2015;13:215.
12. Reichelt AC, Stoeckel LE, Reagan LP, et al. Dietary influences on cognition. *Physiol Behav*. 2018;192:118–126.
13. Francis H, Stevenson R. The longer-term impacts of Western diet on human cognition and the brain. *Appetite*. 2013;63:119–128.
14. Nepal B, Brown LJ, Anstey KJ. Rising midlife obesity will worsen future prevalence of dementia. *PLoS One*. 2014;9:e99305.
15. Cheng G, Huang C, Deng H, et al. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern Med J*. 2012;42:484–491.
16. Agusti A, Garcia-Pardo MP, Lopez-Almela I, et al. Interplay between the gut-brain axis, obesity and cognitive function. *Front Neurosci*. 2018;12:155.
17. Jacka FN, Pasco JA, Mykletun A, et al. Association of Western and traditional diets with depression and anxiety in women. *Am J Psychiatry*. 2010;167:305–311.
18. Kanoski SE, Davidson TL. Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. *Physiol Behav*. 2011;103:59–68.
19. Sofi F, Abbate R, Gensini GF, et al. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr*. 2010;92:1189–1196.
20. Dinan TG, Stanton C, Long-Smith C, et al. Feeding melancholic microbes: MyNewGut recommendations on diet and mood. *Clin Nutr*. 2019;38:1995–2001.
21. Berendsen AAM, Kang JH, van de Rest O, et al. The dietary approaches to stop hypertension diet, cognitive function, and cognitive decline in American older women. *J Am Med Dir Assoc*. 2017;18:427–432.

22. Morris MC, Tangney CC, Wang Y, et al. MIND diet slows cognitive decline with aging. *Alzheimers Dement*. 2015;11:1015–1022.
23. McEvoy CT, Guyer H, Langa KM, et al. Neuroprotective diets are associated with better cognitive function: The Health and Retirement Study. *J Am Geriatr Soc*. 2017;65:1857–1862.
24. Maalouf M, Rho JM, Mattson MP. The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. *Brain Res Rev*. 2009;59:293–315.
25. Prehn K, Jumpertz von Schwartzenberg R, Mai K, et al. Caloric restriction in older adults-differential effects of weight loss and reduced weight on brain structure and function. *Cereb Cortex*. 2017;27:1765–1778.
26. Hallbook T, Ji S, Maudsley S, et al. The effects of the ketogenic diet on behavior and cognition. *Epilepsy Res*. 2012;100:304–309.
27. Uusitupa M, Hermansen K, Savolainen MJ, et al. Effects of an isocaloric healthy Nordic diet on insulin sensitivity, lipid profile and inflammation markers in metabolic syndrome – a randomized study (SYSDIET). *J Intern Med*. 2013;274:52–66.
28. Mannikko R, Komulainen P, Schwab U, et al. The Nordic diet and cognition–the DR's EXTRA Study. *Br J Nutr*. 2015;114:231–239.
29. Willcox DC, Willcox BJ, Todoriki H, et al. The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. *J Am Coll Nutr*. 2009;28(suppl 4):500S–516S.
30. Donato F, Jacobsen RI, Moser MB, et al. Stellate cells drive maturation of the entorhinal-hippocampal circuit. *Science*. 2017;355:eaai8178.
31. Paolicelli RC, Bolasco G, Pagani F, et al. Synaptic pruning by microglia is necessary for normal brain development. *Science*. 2011;333:1456–1458.
32. Hong S, Stevens B. Microglia: phagocytosing to clear, sculpt, and eliminate. *Dev Cell*. 2016;38:126–128.
33. Eriksson PS, Perfilieva E, Bjork-Eriksson T, et al. Neurogenesis in the adult human hippocampus. *Nat Med*. 1998;4:1313–1317.
34. Gage FH. Neurogenesis in the adult brain. *J Neurosci*. 2002;22:612–613.
35. Pilz GA, Bottes S, Betizeau M, et al. Live imaging of neurogenesis in the adult mouse hippocampus. *Science*. 2018;359:658–662.
36. Bourre JM. Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 2: macronutrients. *J Nutr Health Aging*. 2006;10:386–399.
37. Benton D. The influence of children's diet on their cognition and behavior. *Eur J Nutr*. 2008;47:25–37.
38. Keunen K, van Elburg RM, van Bel F, et al. Impact of nutrition on brain development and its neuroprotective implications following preterm birth. *Pediatr Res*. 2015;77:148–155.
39. Nyaradi A, Li J, Hickling S, et al. The role of nutrition in children's neurocognitive development, from pregnancy through childhood. *Front Hum Neurosci*. 2013;7:97.
40. Prado EL, Dewey KG. Nutrition and brain development in early life. *Nutr Rev*. 2014;72:267–284.
41. Piomelli D, Astarita G, Rapaka R. A neuroscientist's guide to lipidomics. *Nat Rev Neurosci*. 2007;8:743–754.
42. Langelier B, Linard A, Bordat C, et al. Long chain-polyunsaturated fatty acids modulate membrane phospholipid composition and protein localization in lipid rafts of neural stem cell cultures. *J Cell Biochem*. 2010;110:1356–1364.
43. Su HM. Mechanisms of n-3 fatty acid-mediated development and maintenance of learning memory performance. *J Nutr Biochem*. 2010;21:364–373.
44. Robson LG, Dyall S, Sidloff D, et al. Omega-3 polyunsaturated fatty acids increase the neurite outgrowth of rat sensory neurones throughout development and in aged animals. *Neurobiol Aging*. 2010;31:678–687.
45. Kitajka K, Sinclair AJ, Weisinger RS, et al. Effects of dietary omega-3 polyunsaturated fatty acids on brain gene expression. *Proc Natl Acad Sci USA*. 2004;101:10931–10936.
46. Urquiza A. M d, Liu S, Sjoberg M, et al. Docosahexaenoic acid, a ligand for the retinoid X receptor in mouse brain. *Science*. 2000;290:2140–2144.
47. Williard DE, Harmon SD, Kaduce TL, et al. Docosahexaenoic acid synthesis from n-3 polyunsaturated fatty acids in differentiated rat brain astrocytes. *J Lipid Res*. 2001;42:1368–1376.
48. Tang M, Zhang M, Cai H, et al. Maternal diet of polyunsaturated fatty acid altered the cell proliferation in the dentate gyrus of hippocampus and influenced glutamatergic and serotoninergic systems of neonatal female rats. *Lipids Health Dis*. 2016;15:71.
49. Giles C, Takechi R, Mellett NA, et al. The effects of long-term saturated fat enriched diets on the brain lipidome. *PLoS One*. 2016;11:e0166964.
50. Glade MJ, Smith K. Phosphatidylserine and the human brain. *Nutrition* 2015;31:781–786.
51. Palmano K, Rowan A, Guillermo R, et al. The role of gangliosides in neurodevelopment. *Nutrients*. 2015;7:3891–3913.
52. Regina Todeschini A, Hakomori SI. Functional role of glycosphingolipids and gangliosides in control of cell adhesion, motility, and growth, through glycosynaptic microdomains. *Biochim Biophys Acta*. 2008;1780:421–433.
53. Martin-Sosa S, Martin MJ, Castro MD, et al. Lactational changes in the fatty acid composition of human milk gangliosides. *Lipids*. 2004;39:111–116.
54. Schnaar RL, Gerardy-Schahn R, Hildebrandt H. Sialic acids in the brain: gangliosides and polysialic acid in nervous system development, stability, disease, and regeneration. *Physiol Rev*. 2014;94:461–518.
55. Gurnida DA, Rowan AM, Idjradinata P, et al. Association of complex lipids containing gangliosides with cognitive development of 6-month-old infants. *Early Hum Dev*. 2012;88:595–601.
56. Guillermo RB, Yang P, Vickers MH, et al. Supplementation with complex milk lipids during brain development promotes neuroplasticity without altering myelination or vascular density. *Food Nutr Res*. 2015;59:25765.
57. Wang B. Molecular mechanism underlying sialic acid as an essential nutrient for brain development and cognition. *Adv Nutr*. 2012;3(suppl 1):465S–472S.
58. Elison E, Vigsnaes LK, Rindom Krogsgaard L, et al. Oral supplementation of healthy adults with 2′-O-fucosyllactose and lacto-N-neotetraose is well tolerated and shifts the intestinal microbiota. *Br J Nutr*. 2016;116:1356–1368.
59. Williams S, Chen L, Savignac HM, et al. Neonatal prebiotic (BGOS) supplementation increases the levels of synaptophysin, GluN2A-subunits and BDNF proteins in the adult rat hippocampus. *Synapse*. 2016;70:121–124.
60. Mattei D, Pietrobelli A. Micronutrients and brain development. *Curr Nutr Rep*. 2019;8:99–107.
61. Kennedy DO. B Vitamins and the brain: mechanisms, dose and efficacy–a review. *Nutrients*. 2016;8:68.
62. Moretti R, Caruso P. The controversial role of homocysteine in neurology: from labs to clinical practice. *Int J Mol Sci*. 2019;20:231.
63. Eyles DW, Burne TH, McGrath JJ. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. *Front Neuroendocrinol*. 2013;34:47–64.
64. Christakos S, Dhawan P, Porta A, et al. Vitamin D and intestinal calcium absorption. *Mol Cell Endocrinol*. 2011;347:25–29.
65. Bading H. Nuclear calcium signalling in the regulation of brain function. *Nat Rev Neurosci*. 2013;14:593–608.
66. Payne ME, Anderson JJ, Steffens DC. Calcium and vitamin D intakes may be positively associated with brain lesions in depressed and nondepressed elders. *Nutr Res*. 2008;28:285–292.
67. Lozoff B, Beard J, Connor J, et al. Long-lasting neural and behavioral effects of iron deficiency in infancy. *Nutr Rev*. 2006;64:34–43; discussion S72–91.
68. Lopez A, Cacoub P, Macdougall IC, et al. Iron deficiency anaemia. *Lancet*. 2016;387:907–916.
69. Gower-Winter SD, Levenson CW. Zinc in the central nervous system: from molecules to behavior. *Biofactors*. 2012;38:186–193.
70. Delange F. Iodine deficiency as a cause of brain damage. *Postgrad Med J*. 2001;77:217–220.
71. Vermiglio F, Lo Presti VP, Moleti M, et al. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. *J Clin Endocrinol Metab*. 2004;89:6054–6060.
72. Calabrese V, Mancuso C, Calvani M, et al. Nitric oxide in the central nervous system: neuroprotection versus neurotoxicity. *Nat Rev Neurosci*. 2007;8:766–775.
73. Lovinger DM. Communication networks in the brain: neurons, receptors, neurotransmitters, and alcohol. *Alcohol Res Health*. 2008;31:196–214.
74. Briguglio M, Dell'Osso B, Panzica G, et al. Dietary neurotransmitters: a narrative review on current knowledge. *Nutrients*. 2018;10:591.
75. Young SN. How to increase serotonin in the human brain without drugs. *J Psychiatry Neurosci*. 2007;32:394–399.
76. Jongkees BJ, Hommel B, Kuhn S, et al. Effect of tyrosine supplementation on clinical and healthy populations under stress or cognitive demands–a review. *J Psychiatr Res*. 2015;70:50–57.
77. Ladero V, Calles-Enriquez M, Fernandez M, et al. Toxicological effects of dietary biogenic amines. *Curr Nutr Food Sci*. 2010;6:145–156.
78. Passani MB, Panula P, Lin JS. Histamine in the brain. *Front Syst Neurosci*. 2014;8:64.
79. Firth J, Marx W, Dash S, et al. The effects of dietary improvement on symptoms of depression and anxiety: a meta-analysis of randomized controlled trials. *Psychosom Med*. 2019;81:265–280.
80. Gangwisch JE, Hale L, Garcia L, et al. High glycemic index diet as a risk factor for depression: analyses from the Women's Health Initiative. *Am J Clin Nutr*. 2015;102:454–463.
81. Roca M, Kohls E, Gili M, et al. Prevention of depression through nutritional strategies in high-risk persons: rationale and design of the MooDFOOD prevention trial. *BMC Psychiatry*. 2016;16:192.
82. Knuppel A, Shipley MJ, Llewellyn CH, et al. Sugar intake from sweet food and beverages, common mental disorder and depression: prospective findings from the Whitehall II Study. *Sci Rep*. 2017;7:6287.
83. Sanchez-Villegas A, Perez-Cornago A, Zazpe I, et al. Micronutrient intake adequacy and depression risk in the SUN cohort study. *Eur J Nutr*. 2018;57:2409–2419.
84. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry*. 2006;67:1954–1967.

85. Liperoti R, Landi F, Fusco O, et al. Omega-3 polyunsaturated fatty acids and depression: a review of the evidence. *Curr Pharm Des*. 2009;15:4165–4172.
86. Ross BM. Omega-3 polyunsaturated fatty acids and anxiety disorders. *Prostaglandins Leukot Essent Fatty Acids*. 2009;81:309–312.
87. Peet M. International variations in the outcome of schizophrenia and the prevalence of depression in relation to national dietary practices: an ecological analysis. *Br J Psychiatry*. 2004;184:404–408.
88. Nabavi SM, Daglia M, Braidy N, et al. Natural products, micronutrients, and nutraceuticals for the treatment of depression: a short review. *Nutr Neurosci*. 2017;20:180–194.
89. Alpert JE, Fava M. Nutrition and depression: the role of folate. *Nutr Rev*. 1997;55:145–149.
90. Boyle NB, Lawton C, Dye L. The effects of magnesium supplementation on subjective anxiety and stress-a systematic review. *Nutrients*. 2017;9:429.
91. Gulyaeva N, Aniol V. Good guys from a shady family. *J Neurochem*. 2012;121:841–842.
92. Casal S. Neuroactive β-carbolines norharman and harman in coffee. In: Preedy VR, ed. *Coffee in Health and Disease Prevention*. San Diego, CA: Academic Press; 2015:737–743.
93. Vignes M, Maurice T, Lante F, et al. Anxiolytic properties of green tea polyphenol (-)-epigallocatechin gallate (EGCG). *Brain Res*. 2006;1110:102–115.
94. Campbell EL, Chebib M, Johnston GA. The dietary flavonoids apigenin and (-)-epigallocatechin gallate enhance the positive modulation by diazepam of the activation by GABA of recombinant GABA(A) receptors. *Biochem Pharmacol*. 2004;68:1631–1638.
95. Lardner AL. Neurobiological effects of the green tea constituent theanine and its potential role in the treatment of psychiatric and neurodegenerative disorders. *Nutr Neurosci*. 2014;17:145–155.
96. Ritsner MS, Miodownik C, Ratner Y, et al. L-theanine relieves positive, activation, and anxiety symptoms in patients with schizophrenia and schizoaffective disorder: an 8-week, randomized, double-blind, placebo-controlled, 2-center study. *J Clin Psychiatry*. 2011;72:34–42.
97. Miodownik C, Maayan R, Ratner Y, et al. Serum levels of brain-derived neurotrophic factor and cortisol to sulfate of dehydroepiandrosterone molar ratio associated with clinical response to L-theanine as augmentation of antipsychotic therapy in schizophrenia and schizoaffective disorder patients. *Clin Neuropharmacol*. 2011;34:155–160.
98. Xu Y, Wang Z, You W, et al. Antidepressant-like effect of trans-resveratrol: involvement of serotonin and noradrenaline system. *Eur Neuropsychopharmacol*. 2010;20:405–413.
99. Wu C, Sun D. GABA receptors in brain development, function, and injury. *Metab Brain Dis*. 2015;30:367–379.
100. Carpentieri A, Diaz de Barboza G, Areco V, et al. New perspectives in melatonin uses. *Pharmacol Res*. 2012;65:437–444.
101. Reiter RJ, Acuna-Castroviejo D, Tan DX, et al. Free radical-mediated molecular damage. Mechanisms for the protective actions of melatonin in the central nervous system. *Ann N Y Acad Sci*. 2006;939:200–215.
102. Peuhkuri K, Sihvola N, Korpela R. Dietary factors and fluctuating levels of melatonin. *Food Nutr Res*. 2012;56:17252.
103. Meng X, Li Y, Li S, et al. Dietary sources and bioactivities of melatonin. *Nutrients*. 2017;9:367.
104. Kaplan BJ, Crawford SG, Field CJ, Simpson JS. Vitamins, minerals, and mood. *Psychol Bull*. 2007;133:747–760.
105. Gutierrez-Monreal MA, Cuevas-Diaz Duran R, Moreno-Cuevas JE, et al. A role for 1α, 25-dihydroxyvitamin D_3 in the expression of circadian genes. *J Biol Rhythms*. 2014;29:384–388.
106. Neuhaus W, Trauner G, Gruber D, et al. Transport of a GABAA receptor modulator and its derivatives from *Valeriana officinalis* L. *s. l.* across an in vitro cell culture model of the blood-brain barrier. *Planta Med*. 2008;74:1338–1344.
107. Patocka J, Jaki J. Biomedically relevant chemical constituents of *Valeriana officinalis*. *J Appl Biomed*. 2010;8:11–18.
108. Bent S, Padula A, Moore D, et al. Valerian for sleep: a systematic review and meta-analysis. *Am J Med*. 2006;119:1005–1012.
109. Shi Y, Dong JW, Zhao JH, et al. Insomnia medications that target GABAergic systems: a review of the psychopharmacological evidence. *Curr Neuropharmacol*. 2014;12:289–302.
110. Srivastava JK, Shankar E, Gupta S. Chamomile: a herbal medicine of the past with bright future. *Mol Med Rep*. 2010;3:895–901.
111. Ngan A, Conduit R. A double-blind, placebo-controlled investigation of the effects of *Passiflora incarnata* (passionflower) herbal tea on subjective sleep quality. *Phytother Res*. 2011;25:1153–1159.
112. Elsas SM, Rossi DJ, Raber J, et al. *Passiflora incarnata* L. (passionflower) extracts elicit GABA currents in hippocampal neurons in vitro, and show anxiogenic and anticonvulsant effects in vivo, varying with extraction method. *Phytomedicine*. 2010;17:940–949.
113. Scholey A, Gibbs A, Neale C, et al. Anti-stress effects of lemon balm-containing foods. *Nutrients*. 2014;6:4805–4821.
114. Kirchgessner AL. Orexins in the brain-gut axis. *Endocr Rev*. 2002;23:1–15.
115. Karnani MM, Apergis-Schoute J, Adamantidis A, et al. Activation of central orexin/hypocretin neurons by dietary amino acids. *Neuron*. 2011;72:616–629.
116. Thakkar MM. Histamine in the regulation of wakefulness. *Sleep Med Rev*. 2011;15:65–74.
117. Ribeiro JA, Sebastiao AM. Caffeine and adenosine. *J Alzheimers Dis*. 2010;20(suppl 1):S3–S15.
118. Smith A, Brice C, Nash J, et al. Caffeine and central noradrenaline: effects on mood, cognitive performance, eye movements and cardiovascular function. *J Psychopharmacol*. 2003;17:283–292.
119. Deslandes AC, Veiga H, Cagy M, et al. Effects of caffeine on the electrophysiological, cognitive and motor responses of the central nervous system. *Braz J Med Biol Res*. 2005;38:1077–1086.
120. Jones G. Caffeine and other sympathomimetic stimulants: modes of action and effects on sports performance. *Essays Biochem*. 2008;44:109–123.
121. Addicott MA, Yang LL, Peiffer AM, et al. The effect of daily caffeine use on cerebral blood flow: how much caffeine can we tolerate? *Hum Brain Mapp*. 2009;30:3102–3114.
122. Muller T. Catechol-*O*-methyltransferase inhibitors in Parkinson's disease. *Drugs* 2015;75:157–174.
123. Dimpfel W, Wiebe J, Gericke N, et al. Zynamite (*Mangifera indica* leaf extract) and caffeine act in a synergistic manner on electrophysiological parameters of rat central nervous system. *Food Nutr Sci*. 2018;09:502–518.
124. Piomelli D, Sasso O. Peripheral gating of pain signals by endogenous lipid mediators. *Nat Neurosci*. 2014;17:164–174.
125. Piomelli D, Hohmann AG, Seybold V, et al. A lipid gate for the peripheral control of pain. *J Neurosci*. 2014;34:15184–15191.
126. Keppel Hesselink JM, de Boer T, Witkamp RF. Palmitoylethanolamide: a natural body-own anti-inflammatory agent, effective and safe against influenza and common cold. *Int J Inflam*. 2013;2013:1–8.
127. Duan L, Yang J, Slaughter MM. Caffeine inhibition of ionotropic glycine receptors. *J Physiol*. 2009;587:4063–4075.
128. Zhang CG, Kim SJ. Taurine induces anti-anxiety by activating strychnine-sensitive glycine receptor in vivo. *Ann Nutr Metab*. 2007;51:379–386.
129. Irsfeld M, Spadafore M, Pruss BM. β-Phenylethylamine, a small molecule with a large impact. *Webmedcentral*. 2013;4:4409.
130. Hanus LO, Mechoulam R. Novel natural and synthetic ligands of the endocannabinoid system. *Curr Med Chem*. 2010;17:1341–1359.
131. Mechoulam R, Parker LA. The endocannabinoid system and the brain. *Annu Rev Psychol*. 2013;64:21–47.
132. Lee JW, Huang BX, Kwon H, et al. Orphan GPR110 (ADGRF1) targeted by *N*-docosahexaenoylethanolamine in development of neurons and cognitive function. *Nat Commun*. 2016;7:13123.
133. Kogan NM, Mechoulam R. Cannabinoids in health and disease. *Dialogues Clin Neurosci*. 2007;9:413–430.
134. Iffland K, Grotenhermen F. An update on safety and side effects of cannabidiol: a review of clinical data and relevant animal studies. *Cannabis Cannabinoid Res*. 2017;2:139–154.
135. Roh E, Song DK, Kim MS. Emerging role of the brain in the homeostatic regulation of energy and glucose metabolism. *Exp Mol Med*. 2016;48:e216.
136. Paul A, Chaker Z, Doetsch F. Hypothalamic regulation of regionally distinct adult neural stem cells and neurogenesis. *Science*. 2017;356:1383–1386.
137. Codagnone MG, Spichak S, O'Mahony SM, et al. Programming bugs: microbiota and the developmental origins of brain health and disease. *Biol Psychiatry*. 2019;85:150–163.
138. Dinan TG, Cryan JF. Brain-gut-microbiota axis and mental health. *Psychosom Med*. 2017;79:920–926.
139. Al-Asmakh M, Anuar F, Zadjali F, et al. Gut microbial communities modulating brain development and function. *Gut Microbes*. 2012;3:366–373.
140. Panduro A, Rivera-Iniguez I, Sepulveda-Villegas M, et al. Emotions and gut microbiota: the next frontier for the gastroenterologist. *World J Gastroenterol*. 2017;23:3030–3042.
141. Baj A, Moro E, Bistoletti M, et al. Glutamatergic signaling along the microbiota-gut-brain axis. *Int J Mol Sci*. 2019;20:1482.
142. Ekstrand B, Young JF, Rasmussen MK. Taste receptors in the gut—a new target for health promoting properties in diet. *Food Res Int*. 2017;100:1–8.
143. Bonaz B, Bazin T, Pellissier S. The vagus nerve at the interface of the microbiota-gut-brain axis. *Front Neurosci*. 2018;12:49.
144. Strandwitz P. Neurotransmitter modulation by the gut microbiota. *Brain Res*. 2018;1693:128–133.
145. Dash S, Clarke G, Berk M, et al. The gut microbiome and diet in psychiatry: focus on depression. *Curr Opin Psychiatry*. 2015;28:1–6.
146. Dickerson F, Severance E, Yolken R. The microbiome, immunity, and schizophrenia and bipolar disorder. *Brain Behav Immun*. 2017;62:46–52.
147. Hills RD Jr, Pontefract BA, Mishcon HR, et al. Gut microbiome: profound implications for diet and disease. *Nutrients*. 2019;11:1613.
148. Fardet A. New hypotheses for the health-protective mechanisms of whole-grain cereals: what is beyond fibre? *Nutr Res Rev*. 2010;23:65–134.
149. Khan NA, Raine LB, Drollette ES, et al. Dietary fiber is positively associated with cognitive control among prepubertal children. *J Nutr*. 2015;145:143–149.

150. Bourassa MW, Alim I, Bultman SJ, et al. Butyrate, neuroepigenetics and the gut microbiome: can a high fiber diet improve brain health? *Neurosci Lett*. 2016;625:56–63.
151. Li M, Santpere G, Imamura Kawasawa Y, et al. Integrative functional genomic analysis of human brain development and neuropsychiatric risks. *Science*. 2018;362:eaat7615.
152. Inoue R, Sakaue Y, Kawada Y, et al. Dietary supplementation with partially hydrolyzed guar gum helps improve constipation and gut dysbiosis symptoms and behavioral irritability in children with autism spectrum disorder. *J Clin Biochem Nutr*. 2019;64:217–223.
153. Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature*. 2008;455:894–902.
154. Crowell MD, Decker GA, Levy R, et al. Gut-brain neuropeptides in the regulation of ingestive behaviors and obesity. *Am J Gastroenterol*. 2006;101:2848–2856; quiz 2914.
155. Karatayev O, Baylan J, Leibowitz SF. Increased intake of ethanol and dietary fat in galanin overexpressing mice. *Alcohol*. 2009;43:571–580.
156. Lang UE, Borgwardt S. Molecular mechanisms of depression: perspectives on new treatment strategies. *Cell Physiol Biochem*. 2013;31:761–777.
157. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368:1696–1705.
158. Velarde-Salcedo AJ, Barrera-Pacheco A, Lara-Gonzalez S, et al. In vitro inhibition of dipeptidyl peptidase IV by peptides derived from the hydrolysis of amaranth (*Amaranthus hypochondriacus* L.) proteins. *Food Chem*. 2013;136:758–764.
159. Lacroix IME, Li-Chan E. Food-derived dipeptidyl-peptidase IV inhibitors as a potential approach for glycemic regulation—current knowledge and future research considerations. *Trends Food Sci Technol*. 2016;54:1–16.
160. Pupovac J, Anderson GH. Dietary peptides induce satiety via cholecystokinin-A and peripheral opioid receptors in rats. *J Nutr*. 2002;132:2775–2780.
161. Teschemacher H. Opioid receptor ligands derived from food proteins. *Curr Pharm Des*. 2003;9:1331–1344.
162. Duraffourd C, De Vadder F, Goncalves D, et al. Mu-opioid receptors and dietary protein stimulate a gut-brain neural circuitry limiting food intake. *Cell*. 2012;150:377–388.
163. Kaelberer MM, Buchanan KL, Klein ME, et al. A gut-brain neural circuit for nutrient sensory transduction. *Science*. 2018;361:eaat5236.
164. Amadio M, Govoni S, Alkon DL, et al. Emerging targets for the pharmacology of learning and memory. *Pharmacol Res*. 2004;50:111–122.
165. Josselyn SA, Tonegawa S. Memory engrams: recalling the past and imagining the future. *Science*. 2020;367:eaaw4325.
166. Rosenzweig ES, Barnes CA. Impact of aging on hippocampal function: plasticity, network dynamics, and cognition. *Prog Neurobiol*. 2003;69:143–179.
167. Greenwood PM, Parasuraman R. Neuronal and cognitive plasticity: a neurocognitive framework for ameliorating cognitive aging. *Front Aging Neurosci*. 2010;2:150.
168. Bruel-Jungerman E, Davis S, Laroche S. Brain plasticity mechanisms and memory: a party of four. *Neuroscientist*. 2007;13:492–505.
169. Murphy T, Dias GP, Thuret S. Effects of diet on brain plasticity in animal and human studies: mind the gap. *Neural Plast*. 2014;2014:1–32.
170. Takei Y. Age-dependent decline in neurogenesis of the hippocampus and extracellular nucleotides. *Hum Cell*. 2019;32:88–94.
171. Slutsky I, Abumaria N, Wu LJ, et al. Enhancement of learning and memory by elevating brain magnesium. *Neuron*. 2010;65:165–177.
172. Frederickson CJ, Koh JY, Bush AI. The neurobiology of zinc in health and disease. *Nat Rev Neurosci*. 2005;6:449–462.
173. Grabrucker AM, Rowan M, Garner CC. Brain-delivery of zinc-ions as potential treatment for neurological diseases: mini review. *Drug Deliv Lett*. 2011;1:13–23.
174. Abbott NJ, Patabendige AA, Dolman DE, et al. Structure and function of the blood-brain barrier. *Neurobiol Dis*. 2010;37:13–25.
175. Vanlandewijck M, He L, Mae MA, et al. A molecular atlas of cell types and zonation in the brain vasculature. *Nature*. 2018;554:475–480.
176. Braniste V, Al-Asmakh M, Kowal C, et al. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med*. 2014;6:263ra158.
177. Mergenthaler P, Lindauer U, Dienel GA, et al. Sugar for the brain: the role of glucose in physiological and pathological brain function. *Trends Neurosci*. 2013;36:587–597.
178. Martin B, Mattson MP, Maudsley S. Caloric restriction and intermittent fasting: two potential diets for successful brain aging. *Ageing Res Rev*. 2006;5:332–353.
179. Guo J, Bakshi V, Lin AL. Early shifts of brain metabolism by caloric restriction preserve white matter integrity and long-term memory in aging mice. *Front Aging Neurosci*. 2015;7:213.
180. Espeland MA, Luchsinger JA, Neiberg RH, et al. Long term effect of intensive lifestyle intervention on cerebral blood flow. *J Am Geriatr Soc*. 2018;66:120–126.
181. Cummings J, Scheltens P, McKeith I, et al. Effect size analyses of souvenaid in patients with Alzheimer's disease. *J Alzheimers Dis*. 2016;55:1131–1139.
182. Mi W, van Wijk N, Cansev M, et al. Nutritional approaches in the risk reduction and management of Alzheimer's disease. *Nutrition*. 2013;29:1080–1089.
183. Broersen LM, Kuipers AA, Balvers M, et al. A specific multi-nutrient diet reduces Alzheimer-like pathology in young adult AβPP$_{swe}$/PS1$_{dE9}$ mice. *J Alzheimers Dis*. 2012;33:177–190.
184. Perez-Pardo P, de Jong EM, Broersen LM, et al. Promising effects of neurorestorative diets on motor, cognitive, and gastrointestinal dysfunction after symptom development in a mouse model of Parkinson's disease. *Front Aging Neurosci*. 2017;9:57.
185. Fotuhi M, Mohassel P, Yaffe K. Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: a complex association. *Nat Clin Pract Neurol*. 2009;5:140–152.
186. Latour A, Grintal B, Champeil-Potokar G, et al. Omega-3 fatty acids deficiency aggravates glutamatergic synapse and astroglial aging in the rat hippocampal CA1. *Aging Cell*. 2013;12:76–84.
187. Solfrizzi V, Frisardi V, Capurso C, et al. Dietary fatty acids in dementia and predementia syndromes: epidemiological evidence and possible underlying mechanisms. *Ageing Res Rev*. 2010;9:184–199.
188. Grimm MO, Kuchenbecker J, Grosgen S, et al. Docosahexaenoic acid reduces amyloid beta production via multiple pleiotropic mechanisms. *J Biol Chem*. 2011;286:14028–14039.
189. Bowman GL, Dodge HH, Mattek N, et al. Plasma omega-3 PUFA and white matter mediated executive decline in older adults. *Front Aging Neurosci*. 2013;5:92.
190. Witte AV, Kerti L, Hermannstadter HM, et al. Long-chain omega-3 fatty acids improve brain function and structure in older adults. *Cereb Cortex*. 2014;24:3059–3068.
191. Sydenham E, Dangour AD, Lim WS. Omega 3 fatty acid for the prevention of cognitive decline and dementia. *Cochrane Database Syst Rev*. 2012;CD005379.
192. Werner T, Kumar R, Horvath I, et al. Abundant fish protein inhibits alpha-synuclein amyloid formation. *Sci Rep*. 2018;8:5465.
193. Croteau E, Castellano CA, Richard MA, et al. Ketogenic medium chain triglycerides increase brain energy metabolism in Alzheimer's disease.*J Alzheimers Dis*. 2018;64:551–561.
194. Rebello CJ, Keller JN, Liu AG, et al. Pilot feasibility and safety study examining the effect of medium chain triglyceride supplementation in subjects with mild cognitive impairment: a randomized controlled trial. *BBA Clin*. 2015;3:123–125.
195. Olson CR, Mello CV. Significance of vitamin A to brain function, behavior and learning. *Mol Nutr Food Res*. 2010;54:489–495.
196. Das UN. Folic acid and polyunsaturated fatty acids improve cognitive function and prevent depression, dementia, and Alzheimer's disease–but how and why? *Prostaglandins Leukot Essent Fatty Acids*. 2008;78:11–19.
197. Clarke R, Bennett D, Parish S, et al. Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials with cognitive data on 22,000 individuals. *Am J Clin Nutr*. 2014;100:657–666.
198. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. *PLoS One*. 2010;5:e12244.
199. Nourhashemi F, Hooper C, Cantet C, et al. Cross-sectional associations of plasma vitamin D with cerebral beta-amyloid in older adults at risk of dementia. *Alzheimers Res Ther*. 2018;10:43.
200. Balion C, Griffith LE, Strifler L, et al. Vitamin D, cognition, and dementia: a systematic review and meta-analysis. *Neurology*. 2012;79:1397–1405.
201. Gugliandolo A, Bramanti P, Mazzon E. Role of vitamin E in the treatment of Alzheimer's disease: evidence from animal models. *Int J Mol Sci*. 2017;18:2504.
202. Belitskaya-Levy I, Dysken M, Guarino P, et al. Impact of apolipoprotein E genotypes on vitamin E and memantine treatment outcomes in Alzheimer's disease. *Alzheimers Dement*. 2018;4:344–349.
203. Browne D, McGuinness B, Woodside JV, et al. Vitamin E and Alzheimer's disease: what do we know so far? *Clin Interv Aging*. 2019;14:1303–1317.
204. Gomez-Pinilla F, Nguyen TT. Natural mood foods: the actions of polyphenols against psychiatric and cognitive disorders. *Nutr Neurosci*. 2012;15:127–133.
205. Rodriguez-Mateos A, Vauzour D, Krueger CG, et al. Bioavailability, bioactivity and impact on health of dietary flavonoids and related compounds: an update. *Arch Toxicol*. 2014;88:1803–1853.
206. Vauzour D. Dietary polyphenols as modulators of brain functions: biological actions and molecular mechanisms underpinning their beneficial effects. *Oxid Med Cell Longev*. 2012;2012:1–16.
207. Nurk E, Refsum H, Drevon CA, et al. Intake of flavonoid-rich wine, tea, and chocolate by elderly men and women is associated with better cognitive test performance. *J Nutr*. 2009;139:120–127.
208. Virgili F, Marino M. Regulation of cellular signals from nutritional molecules: a specific role for phytochemicals, beyond antioxidant activity. *Free Radic Biol Med*. 2008;45:1205–1216.
209. Trebaticka J, Durackova Z. Psychiatric disorders and polyphenols: can they be helpful in therapy? *Oxid Med Cell Longev*. 2015;2015:248529.
210. Arroll MA, Wilder L, Neil J. Nutritional interventions for the adjunctive treatment of schizophrenia: a brief review. *Nutr J*. 2014;13:91.
211. Rabassa M, Cherubini A, Zamora-Ros R, et al. Low levels of a urinary biomarker of dietary polyphenol are associated with substantial cognitive decline over a 3-year period in older adults: the Invecchiare in Chianti Study. *J Am Geriatr Soc*. 2015;63:938–946.

212. Kodali M, Parihar VK, Hattiangady B, et al. Resveratrol prevents age-related memory and mood dysfunction with increased hippocampal neurogenesis and microvasculature, and reduced glial activation. *Sci Rep.* 2015;5:8075.
213. Wang J, Tang C, Ferruzzi MG, et al. Role of standardized grape polyphenol preparation as a novel treatment to improve synaptic plasticity through attenuation of features of metabolic syndrome in a mouse model. *Mol Nutr Food Res.* 2013;57:2091–2102.
214. Panza F, Solfrizzi V, Barulli MR, et al. Coffee, tea, and caffeine consumption and prevention of late-life cognitive decline and dementia: a systematic review. *J Nutr Health Aging.* 2015;19:313–328.
215. Chen WQ, Zhao XL, Hou Y, et al. Protective effects of green tea polyphenols on cognitive impairments induced by psychological stress in rats. *Behav Brain Res*. 2009;202:71–76.
216. Ozarowski M, Mikolajczak PL, Piasecka A, et al. Influence of the *Melissa officinalis* leaf extract on long-term memory in scopolamine animal model with assessment of mechanism of action. *Evid Based Complement Alternat Med*. 2016;2016:1–17.
217. Lindbergh CA, Mewborn CM, Hammond BR, et al. Relationship of lutein and zeaxanthin levels to neurocognitive functioning: an fMRI study of older adults. *J Int Neuropsychol Soc.* 2017;23:11–22.
218. Lu J, Zheng YL, Wu DM, et al. Ursolic acid ameliorates cognition deficits and attenuates oxidative damage in the brain of senescent mice induced by D-galactose. *Biochem Pharmacol*. 2007;74:1078–1090.
219. Liang W, Zhao X, Feng J, et al. Ursolic acid attenuates beta-amyloid-induced memory impairment in mice. *Arq Neuropsiquiatr*. 2016;74:482–488.
220. Nelson TJ, Sun MK, Lim C, et al. Bryostatin effects on cognitive function and PKCε in Alzheimer's disease phase IIa and expanded access trials. *J Alzheimers Dis.* 2017;58:521–535.
221. Goyarzu P, Malin DH, Lau FC, et al. Blueberry supplemented diet: effects on object recognition memory and nuclear factor-kappa B levels in aged rats. *Nutr Neurosci*. 2004;7:75–83.
222. Williams CM, El Mohsen MA, Vauzour D, et al. Blueberry-induced changes in spatial working memory correlate with changes in hippocampal CREB phosphorylation and brain-derived neurotrophic factor (BDNF) levels. *Free Radic Biol Med*. 2008;45:295–305.
223. Rendeiro C, Vauzour D, Kean RJ, et al. Blueberry supplementation induces spatial memory improvements and region-specific regulation of hippocampal BDNF mRNA expression in young rats. *Psychopharmacology*. 2012;223:319–330.
224. Spencer JP. The impact of fruit flavonoids on memory and cognition. *Br J Nutr*. 2010;104: S40–47.
225. Rehnmark A, Strömberg I. Antioxidant-enriched diet affects early microglia accumulation and promotes regeneration of the striatal dopamine system after a 6-hydroxidopamine-induced lesion in a rat. *J Exp Neurosci.* 2012;6:JEN.S10424.
226. Virel A, Rehnmark A, Oradd G, et al. Magnetic resonance imaging as a tool to image neuroinflammation in a rat model of Parkinson's disease–phagocyte influx to the brain is promoted by bilberry-enriched diet. *Eur J Neurosci*. 2015;42:2761–2771.
227. Diaz-Villanueva JF, Diaz-Molina R, Garcia-Gonzalez V. Protein folding and mechanisms of proteostasis. *Int J Mol Sci*. 2015;16:17193–17230.
228. Hetz C, Mollereau B. Disturbance of endoplasmic reticulum proteostasis in neurodegenerative diseases. *Nat Rev Neurosci.* 2014;15:233–249.
229. Kaushik S, Cuervo AM. Proteostasis and aging. *Nat Med.* 2015;21:1406–1415.
230. Rice HC, de Malmazet D, Schreurs A, et al. Secreted amyloid-β precursor protein functions as a $GABA_BR1a$ ligand to modulate synaptic transmission. *Science*. 2019;363:eaao4827.
231. Ciechanover A. Proteolysis: from the lysosome to ubiquitin and the proteasome. *Nat Rev Mol Cell Biol.* 2005;6:79–87.
232. Vidal RL, Matus S, Bargsted L, et al. Targeting autophagy in neurodegenerative diseases. *Trends Pharmacol Sci*. 2014;35:583–591.
233. Jackson MP, Hewitt EW. Cellular proteostasis: degradation of misfolded proteins by lysosomes. *Essays Biochem*. 2016;60:173–180.
234. Yoo BC, Kim SH, Cairns N, et al. Deranged expression of molecular chaperones in brains of patients with Alzheimer's disease. *Biochem Biophys Res Commun*. 2001;280:249–258.
235. Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9:119–128.
236. Klaips CL, Jayaraj GG, Hartl FU. Pathways of cellular proteostasis in aging and disease. *J Cell Biol*. 2018;217:51–63.
237. Lorenzen N, Nielsen SB, Yoshimura Y, et al. How epigallocatechin gallate can inhibit α-synuclein oligomer toxicity in vitro. *J Biol Chem*. 2014;289:21299–21310.
238. Yin F, Jiang T, Cadenas E. Metabolic triad in brain aging: mitochondria, insulin/IGF-1 signalling and JNK signalling. *Biochem Soc Trans*. 2013;41:101–105.
239. Guan J, Gluckman P, Yang PZ, et al. Cyclic glycine-proline regulates IGF-1 homeostasis by altering the binding of IGFBP-3 to IGF-1. *Sci Rep.* 2015;4:4388.
240. Fan D, Alamri Y, Liu K, et al. Supplementation of blackcurrant anthocyanins increased cyclic glycine-proline in the cerebrospinal fluid of Parkinson patients: potential treatment to improve insulin-like growth factor-1 function. *Nutrients*. 2018;10:714.
241. Lauriola M, Paroni G, Ciccone F, et al. Erythrocyte associated amyloid-β as potential biomarker to diagnose dementia. *Curr Alzheimer Res.* 2018;15:381–385.
242. Carnevale D, Mascio G, D'Andrea I, et al. Hypertension induces brain β-amyloid accumulation, cognitive impairment, and memory deterioration through activation of receptor for advanced glycation end products in brain vasculature. *Hypertension*. 2012;60:188–197.
243. Nortley R, Korte N, Izquierdo P, et al. Amyloid β oligomers constrict human capillaries in Alzheimer's disease via signaling to pericytes. *Science*. 2019;365:eaav9518.
244. Caberlotto L, Nguyen TP. A systems biology investigation of neurodegenerative dementia reveals a pivotal role of autophagy. *BMC Syst Biol*. 2014;8:65.
245. Liu YJ, Chern Y. AMPK-mediated regulation of neuronal metabolism and function in brain diseases. *J Neurogenet*. 2015;29:50–58.
246. Salminen A, Kaarniranta K, Haapasalo A, et al. AMP-activated protein kinase: a potential player in Alzheimer's disease. *J Neurochem*. 2011;118:460–474.
247. Wang X, Zimmermann HR, Ma T. Therapeutic potential of AMP-activated protein kinase in Alzheimer's disease. *J Alzheimers Dis.* 2019;68:33–38.
248. Blasko I, Stampfer-Kountchev M, Robatscher P, et al. How chronic inflammation can affect the brain and support the development of Alzheimer's disease in old age: the role of microglia and astrocytes. *Aging Cell*. 2004;3:169–176.
249. Joels M, Karst H, Alfarez D, et al. Effects of chronic stress on structure and cell function in rat hippocampus and hypothalamus. *Stress*. 2004;7:221–231.
250. Swaab DF, Bao AM, Lucassen PJ. The stress system in the human brain in depression and neurodegeneration. *Ageing Res Rev*. 2005;4:141–194.
251. Andreasson K. Prostaglandin signalling in cerebral ischaemia. *Br J Pharmacol*. 2010;160:844–846.
252. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. *JAMA*. 2004;292:2237–2242.
253. Sandi C, Touyarot K. Mid-life stress and cognitive deficits during early aging in rats: individual differences and hippocampal correlates. *Neurobiol Aging*. 2006;27:128–140.
254. Gao Y, Bezchlibnyk YB, Sun X, Wang JF, et al. Effects of restraint stress on the expression of proteins involved in synaptic vesicle exocytosis in the hippocampus. *Neuroscience*. 2006;141:1139–1148.
255. de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. *Nat Rev Neurosci*. 2005;6:463–475.
256. Parker KJ, Schatzberg AF, Lyons DM. Neuroendocrine aspects of hypercortisolism in major depression. *Horm Behav*. 2003;43:60–66.
257. Hammen C. Stress and depression. *Annu Rev Clin Psychol*. 2005;1:293–319.
258. Double KL, Gerlach M, Schunemann V, et al. Iron-binding characteristics of neuromelanin of the human substantia nigra. *Biochem Pharmacol*. 2003;66:489–494.
259. Zecca L, Youdim MB, Riederer P, et al. Iron, brain ageing and neurodegenerative disorders. *Nat Rev Neurosci*. 2004;5:863–873.
260. van der Borght K, Kohnke R, Goransson N, et al. Reduced neurogenesis in the rat hippocampus following high fructose consumption. *Regul Pept*. 2011;167:26–30.
261. Rafati A, Anvari E, Noorafshan A. High fructose solution induces neuronal loss in the nucleus of the solitary tract of rats. *Folia Neuropathol*. 2013;3:214–221.
262. Zhang Q, Li X, Cui X, et al. D-galactose injured neurogenesis in the hippocampus of adult mice. *Neurol Res*. 2005;27:552–556.
263. Wei H, Li L, Song Q, et al. Behavioural study of the D-galactose induced aging model in C57BL/6J mice. *Behav Brain Res*. 2005;157:245–251.
264. Cui X, Zuo P, Zhang Q, et al. Chronic systemic D-galactose exposure induces memory loss, neurodegeneration, and oxidative damage in mice: protective effects of R-α-lipoic acid. *J Neurosci Res.* 2006;84:647–654.
265. Lu J, Wu DM, Zheng YL, et al. Purple sweet potato color alleviates D-galactose-induced brain aging in old mice by promoting survival of neurons via PI3K pathway and inhibiting cytochrome c-mediated apoptosis. *Brain Pathol*. 2010;20:598–612.
266. Gawryluk JW, Wang JF, Andreazza AC, et al. Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. *Int J Neuropsychopharmacol*. 2011;14:123–130.
267. Harrison FE, May JM. Vitamin C function in the brain: vital role of the ascorbate transporter SVCT2. *Free Radic Biol Med*. 2009;46:719–730.
268. Loboda A, Damulewicz M, Pyza E, et al. Role of Nrf2/HO-1 system in development, oxidative stress response and diseases: an evolutionarily conserved mechanism. *Cell Mol Life Sci*. 2016;73:3221–3247.
269. Tavender TJ, Bulleid NJ. Peroxiredoxin IV protects cells from oxidative stress by removing H_2O_2 produced during disulphide formation. *J Cell Sci*. 2010;123:2672–2679.
270. Choi IY, Lee P, Denney DR, et al. Dairy intake is associated with brain glutathione concentration in older adults. *Am J Clin Nutr*. 2015;101:287–293.
271. Farr SA, Poon HF, Dogrukol-Ak D, et al. The antioxidants alpha-lipoic acid and N-acetylcysteine reverse memory impairment and brain oxidative stress in aged SAMP8 mice. *J Neurochem*. 2003;84:1173–1183.
272. Lavoie S, Murray MM, Deppen P, et al. Glutathione precursor, *N*-acetyl-cysteine, improves mismatch negativity in schizophrenia patients. *Neuropsychopharmacology*. 2008;33:2187–2199.
273. Farokhnia M, Azarkolah A, Adinehfar F, et al. *N*-acetylcysteine as an adjunct to risperidone for treatment of negative symptoms in patients with chronic

schizophrenia: a randomized, double-blind, placebo-controlled study. *Clin Neuropharmacol*. 2013;36:185–192.
274. Di Lorenzo A, Nabavi SF, Sureda A, et al. Antidepressive-like effects and antioxidant activity of green tea and GABA green tea in a mouse model of post-stroke depression. *Mol Nutr Food Res*. 2016;60:566–579.
275. Laye S, Nadjar A, Joffre C, et al. Anti-inflammatory effects of omega-3 fatty acids in the brain: physiological mechanisms and relevance to pharmacology. *Pharmacol Rev*. 2018;70:12–38.
276. Johnson RW. Feeding the beast: can microglia in the senescent brain be regulated by diet? *Brain Behav Immun*. 2015;43:1–8.
277. Scapagnini G, Colombrita C, Amadio M, et al. Curcumin activates defensive genes and protects neurons against oxidative stress. *Antioxid Redox Signal*. 2006;8:395–403.
278. Yang F, Lim GP, Begum AN, et al. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. *J Biol Chem*. 2005;280:5892–5901.
279. Balogun E, Hoque M, Gong P, et al. Curcumin activates the haem oxygenase-1 gene via regulation of Nrf2 and the antioxidant-responsive element. *Biochem J*. 2003;371:887–895.
280. Scapagnini G, Vasto S, Abraham NG, et al. Modulation of Nrf2/ARE pathway by food polyphenols: a nutritional neuroprotective strategy for cognitive and neurodegenerative disorders. *Mol Neurobiol*. 2011;44:192–201.
281. Small GW, Siddarth P, Li Z, et al. Memory and brain amyloid and tau effects of a bioavailable form of curcumin in non-demented adults: a double-blind, placebo-controlled 18-month trial. *Am J Geriatr Psychiatry*. 2018;26:266–277.
282. Dei Cas M, Ghidoni R. Dietary curcumin: correlation between bioavailability and health potential. *Nutrients*. 2019;11:2147.
283. Wang J, Ferruzzi MG, Ho L, et al. Brain-targeted proanthocyanidin metabolites for Alzheimer's disease treatment. *J Neurosci*. 2012;32:5144–5150.
284. Russo A, Longo R, Vanella A. Antioxidant activity of propolis: role of caffeic acid phenethyl ester and galangin. *Fitoterapia*. 2002;73(suppl 1):S21–S29.
285. Scapagnini G, Foresti R, Calabrese V, et al. Caffeic acid phenethyl ester and curcumin: a novel class of heme oxygenase-1 inducers. *Mol Pharmacol*. 2002;61:554–561.
286. Scapagnini G, Butterfield DA, Colombrita C, et al. Ethyl ferulate, a lipophilic polyphenol, induces HO-1 and protects rat neurons against oxidative stress. *Antioxid Redox Signal*. 2004;6:811–818.
287. Perluigi M, Joshi G, Sultana R, et al. In vivo protective effects of ferulic acid ethyl ester against amyloid-beta peptide 1-42-induced oxidative stress. *J Neurosci Res*. 2006;84:418–426.
288. Mandel S, Weinreb O, Amit T, et al. Cell signaling pathways in the neuroprotective actions of the green tea polyphenol (-)-epigallocatechin-3-gallate: implications for neurodegenerative diseases. *J Neurochem*. 2004;88:1555–1569.
289. Romeo L, Intrieri M, D'Agata V, et al. The major green tea polyphenol, (-)-epigallocatechin-3-gallate, induces heme oxygenase in rat neurons and acts as an effective neuroprotective agent against oxidative stress. *J Am Coll Nutr*. 2009;28(suppl 4):492S–499S.
290. Zhao J, Moore AN, Redell JB, et al. Enhancing expression of Nrf2-driven genes protects the blood brain barrier after brain injury. *J Neurosci*. 2007;27:10240–10248.
291. Nabavi SF, Braidy N, Orhan IE, et al. *Rhodiola rosea* L. and Alzheimer's disease: from farm to pharmacy. *Phytother Res*. 2016;30:532–539.
292. Braidy N, Behzad S, Habtemariam S, et al. Neuroprotective effects of citrus fruit-derived flavonoids, nobiletin and tangeretin in Alzheimer's and Parkinson's disease. *CNS Neurol Disord Drug Targets*. 2017;16:387–397.
293. Johnson MB, Young AD, Marriott I. The therapeutic potential of targeting substance P/NK-1R interactions in inflammatory CNS disorders. *Front Cell Neurosci*. 2016;10:296.
294. Pinter E, Pozsgai G, Hajna Z, et al. Neuropeptide receptors as potential drug targets in the treatment of inflammatory conditions. *Br J Clin Pharmacol*. 2014;77:5–20.
295. Yamamoto A, Nakamura K, Furukawa K, et al. A new nonpeptide tachykinin NK1 receptor antagonist isolated from the plants of Compositae. *Chem Pharm Bull (Tokyo)*. 2002;50:47–52.
296. Dauncey MJ. Genomic and epigenomic insights into nutrition and brain disorders. *Nutrients*. 2013;5:887–914.
297. Wang D, Liu S, Warrell J, et al. Comprehensive functional genomic resource and integrative model for the human brain. *Science*. 2018;362:eaat8464.
298. An JY, Lin K, Zhu L, et al. Genome-wide de novo risk score implicates promoter variation in autism spectrum disorder. *Science*. 2018;362:eaat6576.
299. Palazidou E. The neurobiology of depression. *Br Med Bull*. 2012;101:127–145.
300. Tiffon C. The impact of nutrition and environmental epigenetics on human health and disease. *Int J Mol Sci* 2018;19:3425.
301. Rajarajan P, Borrman T, Liao W, et al. Neuron-specific signatures in the chromosomal connectome associated with schizophrenia risk. *Science*. 2018;362:eaat4311.
302. Girault JA. Epigenetic tinkering with neurotransmitters. *Science*. 2020;368:134–135.
303. Lepack AE, Werner CT, Stewart AF, et al. Dopaminylation of histone H3 in ventral tegmental area regulates cocaine seeking. *Science*. 2020;368:197–201.
304. McGowan PO, Meaney MJ, Szyf M. Diet and the epigenetic (re)programming of phenotypic differences in behavior. *Brain Res*. 2008;1237:12–24.
305. Penner MR, Roth TL, Barnes CA, et al. An epigenetic hypothesis of aging-related cognitive dysfunction. *Front Aging Neurosci* 2010;2:9.
306. Barter JD, Foster TC. Aging in the brain: new roles of epigenetics in cognitive decline. *Neuroscientist*. 2018;24:516–525.
307. Choi SW, Friso S. Epigenetics: a new bridge between nutrition and health. *Adv Nutr*. 2010;1:8–16.
308. Kerek R, Geoffroy A, Bison A, et al. Early methyl donor deficiency may induce persistent brain defects by reducing Stat3 signaling targeted by miR-124. *Cell Death Dis*. 2013;4:e755.
309. Coppede F. One-carbon metabolism and Alzheimer's disease: focus on epigenetics. *Curr Genomics*. 2010;11:246–260.
310. Bishop KS, Ferguson LR. The interaction between epigenetics, nutrition and the development of cancer. *Nutrients*. 2015;7:922–947.
311. St-Laurent-Thibault C, Arseneault M, Longpre F, et al. Tyrosol and hydroxytyrosol, two main components of olive oil, protect N2a cells against amyloid-beta-induced toxicity. Involvement of the NF-κB signaling. *Curr Alzheimer Res*. 2011;8:543–551.
312. Angeloni C, Malaguti M, Barbalace MC, et al. Bioactivity of olive oil phenols in neuroprotection. *Int J Mol Sci* 2017;18:2230.