Symposium on 'Early nutrition and later disease: current concepts, research and implications'

New insights into nutrition and cognitive neuroscience

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Nutrition can affect the brain throughout the life cycle, with profound implications for mental health and degenerative disease. Many aspects of nutrition, from entire diets to specific nutrients, affect brain structure and function. The present short review focuses on recent insights into the role of nutrition in cognition and mental health and is divided into four main sections. First, the importance of nutritional balance and nutrient interactions to brain health are considered by reference to the Mediterranean diet, energy balance, fatty acids and trace elements. Many factors modulate the effects of nutrition on brain health and inconsistencies between studies can be explained in part by differences in early environment and genetic variability. Thus, these two factors are considered in the second and third parts of the present review. Finally, recent findings on mechanisms underlying the actions of nutrition on the brain are considered. These mechanisms involve changes in neurotrophic factors, neural pathways and brain plasticity. Advances in understanding the critical role of nutrition in brain health will help to fulfil the potential of nutrition to optimise brain function, prevent dysfunction and treat disease.

Brain function and cognition: Early development: Mental health and disease: Nutrigenomics and nutrigenetics

The role of nutrition in cognitive neuroscience is complex because, as with all aspects of nutrition, it is multifactorial. The concern is not simply with the impact of a single chemical on the brain but with multiple nutrients, metabolites and interacting factors. Nevertheless, despite many controversies, themes are emerging and underlying mechanisms are being elucidated. This position is in part a result of major advances in many areas of the biological sciences and the development of new techniques in molecular biology and brain imaging.

Cognition refers to the mental processes involved in acquiring knowledge and the integration of these processes into responses such as learning, attention, memory, intelligence (intelligence quotient; IQ) and consciousness. Many aspects of nutrition, from entire diets to individual nutrients, have been implicated in cognition, mental health, dysfunction and disease[1–5]. It is not surprising that nutrition affects cognition and mental health because brain structure and function are ultimately dependent on nutritional input. However, it is difficult to assess the precise actions of specific dietary components because individuals eat foods and diets, not individual nutrients. Nevertheless, numerous studies have shown that many aspects of cognition are affected by nutrition, including memory, IQ, attention-deficit hyperactivity disorder, dyslexia, depression, schizophrenia, dementia, Alzheimer's disease and Parkinson's disease[1–5].

In recent years advances have been made in several key areas of nutrition and cognitive neuroscience. Nutritional interactions and the balance between specific nutritional components are recognised to be of critical importance, and considerable progress has been made in relation to energy balance, fatty acids and trace elements. Numerous inconsistencies have been reported between studies on nutrition, cognition and mental health, which can be accounted for by many factors, including differences in study design. Recent research suggests that two other factors are of particular importance: early
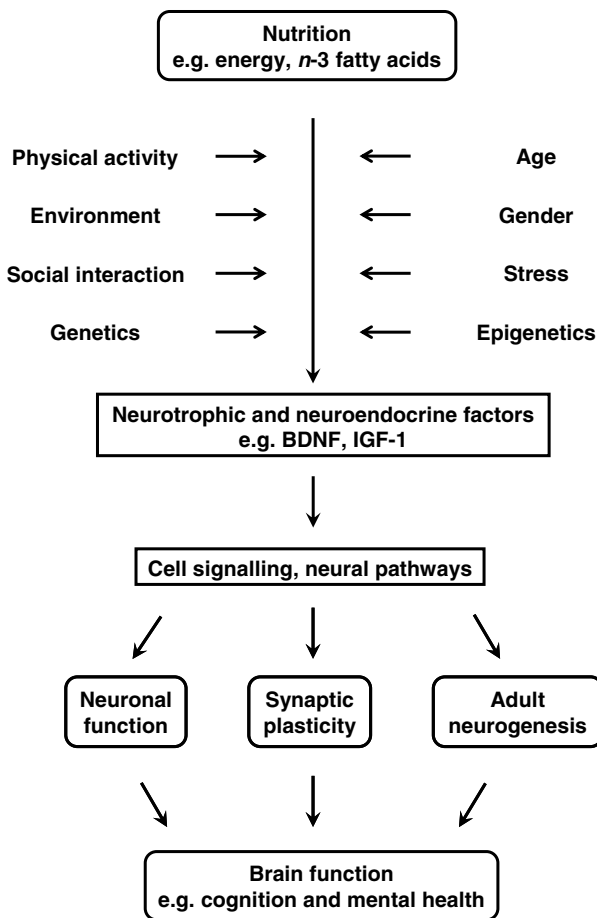
Fig. 1. Outline of mechanisms linking nutrition to brain function and mental health. Multiple cell signalling systems and neural pathways mediate the actions of nutrition on cognition and mental health. Neurotrophic and neuroendocrine factors play key roles in this response. For example, energy balance and n-3 fatty acids act via brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1) to alter expression of numerous genes involved in neuronal function, plasticity and neurogenesis. →, ←, Examples of the many factors that modulate the actions of nutrition on brain function.

environment; genetic variability. Early nutrition profoundly influences mental health in later life, and multiple gene variants markedly alter cognitive responses to nutrition. Understanding of the molecular mechanisms linking nutrition to brain function and mental health is increasing, especially in relation to multiple cell signalling pathways. These mechanisms involve growth factors, hormones and genes important for neurological function. Deeper understanding of these mechanisms, outlined in Fig. 1, should lead to a clearer definition of optimal nutrition for cognition and mental health.

Nutritional balance and brain health

Marked interactions occur between different dietary components, and it is becoming increasingly clear that the balance between specific nutritional factors plays a key role in cognitive function. Recent findings will be illustrated by reference to the Mediterranean diet, energy balance, n-3 and n-6 fatty acids and the trace elements Cu and Zn.

Mediterranean diet

In recent years considerable attention has focused on the role of the Mediterranean diet in cognition and mental health. Precise definition of this diet varies between studies. In general, it is characterised by high intakes of vegetables, fruits, cereals, fish and unsaturated fats such as olive oil, a low to moderate intake of wine during meals and low intakes of red and processed meats, dairy foods and saturated fats. Differences in mental health linked with the Mediterranean diet are probably related in part to nutritional balance, both of different foods and of specific nutrients.

Comprehensive analysis of several studies has shown that higher adherence to the Mediterranean diet reduces the risk of Alzheimer's and Parkinson's diseases by 13%, suggesting clinical relevance for public health[6]. Particularly important is the finding that this diet is also associated with reduced risk of developing mild cognitive impairment and of its conversion to Alzheimer's disease[7]. In the latter study adjustments were made for many variables such as age, energy intake and BMI. However, the authors could not exclude the possibility that physical activity may partially account for some of the effects of the Mediterranean diet.

Energy balance

There are numerous links between energy balance and the brain; not only does the brain have a key role in regulation of energy intake and energy expenditure[8,9], but energy intake and physical activity influence brain structure and function[10].

Considerable evidence demonstrates a close link between energy balance and mental health. The importance of physical activity to mental health is now well recognised[11–13]. It decreases the risk of depression and improves mood and self-esteem. Moreover, regular aerobic exercise increases brain volume and reduces the risk of cognitive impairment, dementia and Alzheimer's disease in older adults.

Moderate undernutrition reduces age-related deficits in cognitive function, whereas overnutrition increases oxidative damage, reduces synaptic plasticity and decreases cognitive function[14]. High-energy diets and a sedentary lifestyle are leading to increased prevalence of obesity and diabetes. These conditions are linked with impaired cognitive function and risk of depression and dementia[15]. Moreover, patients with mental illnesses such as schizophrenia and bipolar disorder have increased incidence of metabolic syndrome and associated obesity, type 2 diabetes and dyslipidaemia[16]. Multiple mechanisms, involving chronic inflammation, cell signalling pathways and genetic factors, link overnutrition with numerous disorders including CVD and Alzheimer's disease[17,18].

Fatty acids: n-3 and n-6

Despite some controversy, substantial evidence suggests a vital role for *n*-3 PUFA in cognition and mental health[19–21]. These fatty acids enhance memory, mood and behaviour and reduce the symptoms of depression. By contrast, deficiency of *n*-3 fatty acids is linked with increased risk of dyslexia, attention-deficit hyperactivity disorder, depression, dementia, Alzheimer's disease and schizophrenia. Moreover, diets high in *trans*- and saturated fats adversely affect cognitive function[22].

The *n*-3 fatty acids include α-linolenic acid (18:3*n*-3), EPA (20:5*n*-3) and DHA (22:6*n*-3). The latter has an especially important role in optimising brain structure and function[23,24]. The actions of DHA are mediated in part by effects on cell membrane structure and energy metabolism. Higher levels of brain DHA increase membrane flexibility and protein–lipid interactions, leading to enhanced neuronal activity and cognition. DHA also has a protective role via its effects on inflammation, oxidative stress and cytokine release. By contrast, decreased DHA in the developing brain is associated with impairments in neurogenesis, neurotransmitter metabolism, learning and memory.

It has long been recognised that fatty acid intake affects the fatty acid content of the body, and maternal intake is reflected in newborn and breast-fed infants[25,26]. Foods high in α-linolenic acid include vegetable oils such as linseed, soyabean and rapeseed and meat from grass-fed animals. However, conversion of α-linolenic acid to EPA and then to DHA is extremely inefficient. Optimal amounts of EPA and DHA therefore have to be provided by an adequate dietary intake, e.g. from fish. Current interest focuses on mechanisms for enhancing *n*-3 fatty acids in the food supply. These mechanisms include modification of meat and milk composition by standard methods of animal husbandry and the use of transgenic techniques for developing plants that produce *n*-3 fatty acids[27].

Recent research suggests that it is not simply the level of *n*-3 fatty acids but the balance between *n*-3 and *n*-6 fatty acid intakes that is critical for optimal mental health[24]. Competitive inhibition occurs between these two groups of fatty acids and Western diets low in *n*-3 fatty acids and high in *n*-6 fatty acids may contribute to reduced accretion of DHA, inhibition of secondary neurite growth and impaired brain development and function.

Not only does the balance within specific nutrient groups affect cognition, but interactions also occur between different groups of nutrients. Thus, a high intake of dietary Cu is associated with cognitive decline if it is combined with a high intake of saturated and *trans*-fats[28].

Trace elements: copper and zinc

Trace elements are of widespread neurological importance and yet are frequently overlooked in studies on nutrition and cognitive function. For example, Cu and Zn have critical actions in neurodevelopment, neurotransmitter synthesis, energy metabolism, antioxidant defence and DNA synthesis[29–31]. Thus, it is not surprising that these trace elements are important for cognitive function. Low plasma Cu is linked with the cognitive decline of Alzheimer's disease and Zn deficiency is linked with attention-deficit hyperactivity disorder in children, impaired memory and learning in adolescents and stress, depression and cognitive decline in adults[4,32].

Trace elements occur in many foods and in healthy individuals on a well-balanced diet the risk of trace element imbalance and subsequent cognitive impairment is low. Good sources of Cu are liver, seafood, nuts, wholegrain cereals, legumes and chocolate, while Zn is abundant in lean red meat, liver, seafood and dairy products[33]. Recent findings suggest that optimal plasma concentrations of Cu, Zn and Fe exist for optimal cognitive function in older adults, with results being gender specific[34]. Moreover, there is a fine balance between the beneficial and harmful effects of many trace elements. In patients with Alzheimer's disease Cu homeostasis is disrupted and this factor may be the trigger for increased oxidative stress and neurodegeneration[35].

Interactions between trace elements may have profound importance for optimal mental health. Deficiency of Zn affects approximately 30% of the world's population and can be a major factor affecting cognition in pregnant women[36]. However, although Zn supplementation alleviates symptoms of deficiency, it can reduce Cu absorption and may result in Cu deficiency and neurological disorders[37]. Such interactions may be especially important for the cognitive development of small preterm infants. These children are born with inadequate stores of Fe, Cu and Zn[38,39] and are frequently given Fe supplementation but no additional source of Cu or Zn.

Nutrition–age interactions and brain health

Many factors modulate the effects of nutrition on mental health, including age (Fig. 1). Early-life experience is of particular importance; in adults the incidence of mental disorders and disease may be related in part to early nutrition. Both prenatal and postnatal nutrition can affect mental health and the incidence of disease in later life, and these effects may even be passed to subsequent generations[40–43].

Critical periods of development

Programming is the phenomenon whereby an insult, such as malnutrition, acting during a critical period has long-term or permanent effects on structure and function. Both the timing and type of insult are important to later brain function. Critical periods of neurodevelopment occur during prenatal and postnatal life, indicating that optimal nutrition is especially important during these early stages of the life cycle[10]. The precise timing of critical periods is related to brain region and anatomical function. For example, in adults who were developing during the atomic bombing of Hiroshima and Nagasaki brain damage and mental retardation were greatest in those who experienced radiation at 8–15 weeks of gestation[44]. During this period

there is rapid proliferation of neuronal elements and neuroblast migration to the cerebral cortex.

Less severe but nevertheless important effects on adult cognition and mental health are associated with early environment, including nutrition. However, most studies in adults do not account for early environmental experiences. The probability is that these experiences account in part for some of the individual differences in adult cognitive responses to nutrition.

Early nutrition and later mental function

Intrauterine growth restriction reflects a reduction in nutrient supply to the fetus, and infants born both small for gestational age and preterm have many nutritional deficits. This outcome has both immediate and long-term consequences for mental health. Recent findings show these infants to be at major risk of impaired neurodevelopment and neurobehaviour, including multiple cognitive deficits in memory and learning[45–47].

Not only are very small infants at risk but size at birth, across the weight range, is related to long-term cognitive function and mental health[48]. Despite some inconsistencies between studies, effects on IQ, depression, attention-deficit hyperactivity disorder and schizophrenia have been documented[48]. There are gender-specific differences, with males being affected more than females. Mechanisms underlying these effects involve changes in neurodevelopment and neuroendocrine systems such as the hypothalamic–pituitary–adrenal axis, growth hormones and thyroid hormones.

Despite considerable controversy, substantial evidence suggests that both maternal and infant nutrition have a critical role in later brain function. Maternal n-3 fatty acid intake at 32 weeks of gestation is directly related to the child's IQ at 8 years[49]. Moreover, breast-fed infants have a greater IQ at 6·5 years[50]. This outcome cannot be entirely a result of social and behavioural differences associated with breast-feeding, because IQ is also greater at 8 years in preterm infants who were tube-fed expressed breast milk[51]. The possibility is that essential fatty acids and growth factors in human milk are involved in this response.

Particularly important are recent findings that early nutrition affects brain structure as well as cognitive function in later life. The hippocampus has an important role in cognition and memory, and preterm infants with intrauterine growth restriction have a reduced hippocampal volume at term age, as well as less-mature brain function[52]. Potential mechanisms include placental insufficiency, increased maternal glucocorticoids and micronutrient deficiency. Optimisation of infant nutrition has long-term beneficial effects on brain structure and function. Preterm infants given a high-nutrient formula have a greater IQ as adolescents than those fed standard formula[53]. The difference in IQ is greater in boys than girls and is accompanied by structural changes; the volume of caudate nuclei is greater in those fed a high-nutrient formula as infants. The extent to which these differences persist into adult life now needs to be investigated.

Nutrition–gene interactions and brain health

Individual variability in responses to nutrition can undoubtedly explain some inconsistencies between studies on nutrition, cognition and mental health. With energy balance, for example, there are marked individual differences in appetite control, RMR and spontaneous activity[54]. Gene variants involving single nucleotides markedly affect cognitive responses to nutrition. Moreover, recent studies on variants involving multiple copies or deletions of DNA sequences suggest that these variants may be especially relevant to individual responses to nutrition. Current research also focuses on the extent to which epigenetics, i.e. heritable changes in gene expression that do not involve a change in DNA sequence, is involved in mediating the long-term effects of nutrition on the brain.

Single-nucleotide polymorphisms

Single-nucleotide polymorphisms are a powerful tool for investigating the role of nutrition in health and disease[55,56]. Numerous investigations, including many on fats, trace elements and energy balance, have highlighted the importance of single-nucleotide polymorphisms in neural and cognitive responses to nutrition.

It is well-established that a variant of *APOE*, a gene essential for lipid transport, is linked with Alzheimer's disease. More recently, it has been found that a variant of *FADS2*, a gene (encoding fatty acid desaturase 2) that is involved in the control of fatty acid pathways, modifies the relationship between infant feeding and IQ[57]. Many genes have been implicated in the regulation of energy balance and obesity[58,59], providing a mechanistic link between energy status and mental health via neuronal control of energy intake and energy expenditure. Complex interactions occur between these genes and their multiple actions in energy balance. Leptin, *FTO* and melanocortin 4 receptor genes appear to control both appetite and spontaneous activity[54,60]. Moreover, common variants of the melanocortin 4 receptor gene add to the effect of the *FTO* gene in the control of body weight[61]. Furthermore, recent research suggests that melanocortins could be used as therapeutic neuroprotective agents, since they act via their receptors to exert anti-inflammatory effects in injured brain cells[62].

Gene–gene interactions, termed epistasis, add further to the complexity of this field. Detailed assessment of Cu, Zn and Fe in the hippocampus shows that polygenic influences underlie altered homeostasis and neurological disease[29]. As epistasis can alter the effect of a genetic variant on phenotype, it can be of limited value to measure the effect of one single-nucleotide polymorphism unless the genomic background is also assessed.

Copy number variants

In recent years considerable insight has been gained into the importance of copy number variants in determining genetic variation[63,64]. These structural variants are common in the human genome and involve multiple copies or deletions of DNA sequences that can affect from 1 kb to

many megabases of DNA per event. These insertions or deletions occur in genes, parts of genes and outside genes and they are linked with genes involved in molecular–environment interactions. Thus, it is highly probable that interactions between environmental factors such as nutrition, single-nucleotide polymorphisms and copy number variants play a critical role in determining cognitive ability, mental health and neurodegenerative disease.

Epigenetics

Recent research suggests that epigenetics plays a key role in the early nutritional programming of long-term cognition and mental health[65,66]. Two major components of epigenetic regulation are DNA methylation and histone acetylation. The former represses gene activity, while the latter increases gene activity, via chromatin remodelling. The epigenetic marking of genes is quite persistent, and the effects of early nutrition on cognition and mental health may be passed between generations via epigenetic mechanisms that modify DNA function but not sequence.

The environment exerts a powerful effect on epigenetic regulation and alterations can occur during the lifetime of identical twins, resulting in differences in gene expression between closely-related individuals. These differences may be critical for brain function; epigenetic mechanisms have been implicated in cognitive function, memory and mental health[67]. These recent studies suggest that nutrition probably has marked influences on the epigenetic programming of brain health and cognition.

Mechanisms underlying nutrition and brain health

It is well recognised that nutrition affects many aspects of brain function including cell membranes, metabolites, enzymes and neurotransmitters[10]. Considerable progress has now been made in understanding the molecular mechanisms and neural pathways underlying the effects of nutrition on mental health. Cellular and nuclear receptors play a key role in mediating nutritional effects on function[56,68–70]. They enable sophisticated regulation of numerous genes involved in neural function and brain plasticity. Nutrients such as fatty acids have receptors in the cell nucleus and thus act directly to affect multiple actions in the brain, by regulating the transcription of numerous genes involved in structure and function. By contrast, energy balance and metabolites affect gene expression indirectly via changes in cell signalling molecules that regulate transcription.

Neurotrophic and neuroendocrine factors

Many nutritional actions on mental health are mediated by neurotrophic and neuroendocrine regulators of brain function. These regulators include brain-derived neurotrophic factor, insulin-like growth factor-1 and glucocorticoids. For example, brain-derived neurotrophic factor acts via TrkB receptors to affect cell signalling pathways, neurogenesis, neuroprotection, learning and memory[18].

Nutritional status affects many growth factors and hormones, which can act as nutritional signals to influence numerous biological systems via changes in gene expression[68]. For example, brain-derived neurotrophic factor and insulin-like growth factor-1 play key roles in mediating the effects of energy balance and n-3 fatty acids on brain health by activating cell signalling systems linked to transcription of genes involved in synaptic plasticity[14]. Similarly, the effects of exercise on cognition can be explained in part by its specific induction of brain-derived neurotrophic factor gene expression in the hippocampus[71].

Critical interactions occur between nutrition and many other factors in regulation of neural pathways (Fig. 1). Dietary DHA supplements enhance the effects of exercise on synaptic plasticity and cognition[72]. Exercise and oestrogen up regulate many of the same biochemical markers in the brain that increase cognitive and neural plasticity; brain-derived neurotrophic factor increases with exercise and oestrogen replacement and the effects are synergistic[73].

Brain plasticity and adult neurogenesis

The brain has considerable neural, synaptic and cognitive plasticity to adapt not only to neural damage but also to nutrition. For example, energy balance and n-3 fatty acids have marked effects on synaptic plasticity via changes in gene expression of neurotrophic factors (Fig. 1). Molecular evolution of the synaptic proteome, including changes in receptors, cytoskeletal proteins and adhesion proteins, has enabled complex brain function to develop[74]. Analysis of the complex interactions between nutrition and the synaptic proteome suggests a promising area for future research.

Adult neurogenesis is currently of considerable research interest, and recent studies have shown that it is physiologically important in the hippocampus; adult-born neurones can form functional synapses with target cells[75]. Important links exist between energy metabolism, glucocorticoids and adult neurogenesis. Thus, a highly important finding is that cognitive impairment in diabetes may result from glucocorticoid-mediated deficits in neurogenesis and synaptic plasticity[76]. By contrast, exercise and dietary restriction exert anti-diabetic effects and can enhance synaptic plasticity and neurogenesis.

Lifestyle, stress and social interaction can also alter nutritional effects on mental health, and this process is probably mediated in part by glucocorticoids[77]. Elevated glucocorticoid levels are associated with poor cognitive ability in individuals subjected to psychosocial stress[78], during normal ageing[79] and in Alzheimer's disease[80]. The possibility, therefore, is that these effects are exerted via changes in brain plasticity and neurogenesis.

Recent studies are also providing new insights into the role of white matter (the brain region underlying the grey matter cortex) in plasticity and cognitive function[81]. Changes in myelin genes and alterations in structure of white matter occur in many psychiatric disorders. Moreover, myelination continues for many decades in the human brain and can change with environmental experience[81–83]. This outcome suggests a novel and potentially

important role for nutrition in regulating myelin plasticity and mental health.

Concluding remarks

Recent studies on the balance and interactions between nutritional components have markedly advanced understanding of the critical role of nutrition in cognition and mental health. The extent to which other factors, such as age and genetics, modulate responses to nutrition is also revealing new insights into its complex actions in brain function. The effects of nutrition on brain plasticity and adult neurogenesis are important areas for future research. They suggest potential mechanisms by which specific nutritional components could be used to improve brain function. Early nutrition is especially critical for long-term cognitive function and mental health. However, recent findings on plasticity and neurogenesis suggest that nutrition throughout the life cycle could be used to optimise brain function, prevent dysfunction and treat disease. Vulnerable groups include not just the very young and the very old, but also those who for many reasons have suboptimal nutritional status at different ages. Considerable evidence suggests that incorporation of advice on diet and physical activity will undoubtedly be of benefit in optimising mental health.

Other potentially important directions for the future include the roles of genomics and epigenomics in modulating the effects of nutrition on the brain and mental health. In the long term, personalised nutrition, based on individual genetic variability and environmental susceptibility, should help to optimise brain function and prevent or alleviate mental disorders. Considerably more research is needed to elucidate the complex interactions between nutrition and numerous variables such as environment, genetics, age and lifestyle in determining cognition and mental health. New genomic technologies and sophisticated imaging techniques are central to recent advances in cognitive neuroscience. Combining these techniques with classical nutrition studies should result in long-term benefits for optimal brain health, longevity and quality of life.

Acknowledgements

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