Proceedings of the Nutrition Society (2012), **71**, 581–591 doi:10.1017/S0029665112000237
 First published online 3 May 2012

The 4th International Symposium of the Nutrition Society was part of the 12th International Congress of Nutrition, Longevity and Quality of Life, Mega Evento Nutrição held at Centro de Convenções e Eventos Frei Caneca, São Paulo, Brazil on 6–8 October 2011

Symposium on 'Nutrition, genes and health: current knowledge and future directions'

Recent advances in nutrition, genes and brain health*

M. J. Dauncey
Wolfson College, University of Cambridge, Cambridge, UK

Molecular mechanisms underlying brain structure and function are affected by nutrition throughout the life cycle, with profound implications for health and disease. Responses to nutrition are in turn influenced by individual differences in multiple target genes. Recent advances in genomics and epigenomics are increasing understanding of mechanisms by which nutrition and genes interact. This review starts with a short account of current knowledge on nutrition–gene interactions, focusing on the significance of epigenetics to nutritional regulation of gene expression, and the roles of SNP and copy number variants (CNV) in determining individual responses to nutrition. A critical assessment is then provided of recent advances in nutrition–gene interactions, and especially energy status, in three related areas: (i) mental health and well-being, (ii) mental disorders and schizophrenia, (iii) neurological (neurodevelopmental and neurodegenerative) disorders and Alzheimer's disease. Optimal energy status, including physical activity, has a positive role in mental health. By contrast, sub-optimal energy status, including undernutrition and overnutrition, is implicated in many disorders of mental health and neurology. These actions are mediated by changes in energy metabolism and multiple signalling molecules, e.g. brain-derived neurotrophic factor (BDNF). They often involve epigenetic mechanisms, including DNA methylation and histone modifications. Recent advances show that many brain disorders result from a sophisticated network of interactions between numerous environmental and genetic factors. Personal, social and economic costs of sub-optimal brain health are immense. Future advances in understanding the complex interactions between nutrition, genes and the brain should help to reduce these costs and enhance quality of life.

Energy intake and physical activity: Genomics and epigenomics: Mental health and well-being: Neurological and mental disorders: Nutrition–gene interactions

Nutrition–gene interactions play a key role in modifying cell structure and function in the brain[1,2]. This can lead to major effects on brain health, dysfunction and disease. Fundamentally, the effects of nutrition on the brain are mediated by changes in gene expression. These changes have many and varied characteristics. They may be dynamic and short-term, stable and long-term, and even heritable between cell divisions and across generations. Moreover, genetic variability can significantly modify the effects of nutrition on gene expression (Fig. 1). Individual differences in responses to nutrition are due in part to common gene variants involving either single nucleotides or large sections of genomic DNA.

Many nutrients, foods and diets are implicated in brain health[1–8]. These include macronutrients, micronutrients, phytochemicals, the Mediterranean diet and energy status, i.e. energy intake, physical activity and energy metabolism. In 1903, it was recognised that energy intake, physical activity and heredity are important for brain health and longevity: '... the impairment of the brain structure and

Abbreviations: BDNF, brain-derived neurotrophic factor; CNV, copy number variant; IUGR, intrauterine growth restriction.

Corresponding author: Dr M. J. Dauncey, email mjd4@cam.ac.uk

*A Portuguese version of this paper is published as two articles in *Nutricão em Pauta*, Brazil (2012).

functions . . . is in many families hereditary; but it is to some degree preventable by great moderation in food and stimulants, by regular physical exercise . . .'[9]. Research during the last century elucidated many of the mechanisms underlying these actions. In the last few years, new genomic and epigenomic technologies have significantly advanced understanding of the importance of nutrition and genes in brain health and disease.

Sub-optimal brain health is associated with numerous disorders of mental health and neurology (neurodevelopmental and neurodegenerative). Distinction between these categories is not always precise. Nevertheless, it is valuable in relation to the diagnosis and treatment of specific brain disorders. The present critical review focuses on recent advances in the role of energy status–gene interactions in three major areas of brain health: mental health and well-being, mental disorders and schizophrenia, and neurological disorders and Alzheimer's disease. These have been chosen as paradigms for the critical role of nutrition–gene interactions in determining brain health throughout life.

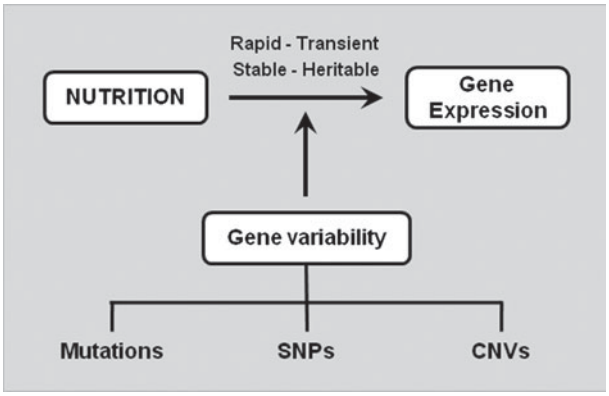

Fig. 1. Outline of nutrition–gene interactions. Nutrition has major influences on gene expression and therefore on structure and function of multiple organs, tissues and systems, including the brain. Regulation is via epigenetic and non-epigenetic mechanisms. Individual variability in multiple genes significantly influences the effects of nutrition on gene expression. Gene variants include relatively rare mutations, and relatively common SNP and copy number variants (CNV).

Nutrition–gene interactions

Nutrigenomics and nutrigenetics

Molecular and cellular mechanisms underlie all aspects of nutrition–gene interactions. The understanding of the mechanisms by which nutrition and genes interact to modify biological structure and function has advanced considerably in recent years. This has been accompanied by a wide range of sometimes confusing terminologies and definitions. In general, the following terms are often used: nutrigenomics refers to the effects of nutrition on gene expression, nutrigenetics refers to the effects of genetic variability on responses to nutrition, and nutritional genomics considers both these aspects[10–12].

Significant advances in techniques of molecular and cellular biology over the last decade have revolutionised approaches to the science of nutrition. Studies on the role of nutrition in health and disease now involve genomics, epigenomics, post-translational modifications, proteomics, metabolomics and systems biology[13–17]. Moreover, comprehensive analyses of genetic variability are advancing understanding of individual differences in responses to nutrition. Together, these approaches are ensuring a more targeted approach to the definition of optimal nutrition throughout the life-cycle.

Nutrition and gene expression: epigenetics

Nutrition affects gene expression at levels of transcription, translation and post-translational modifications. It is now appreciated that epigenetic mechanisms play a key role in some of these responses. The term epigenetics means literally 'above genetics' and refers to mechanisms that induce changes in gene expression without changes in DNA sequence. These mechanisms often include chemical marking of chromatin, the form in which DNA is packaged with histone proteins in the cell nucleus[18]. Epigenetic marks induce chromatin remodelling and related changes in gene expression. They include DNA methylation that reduces gene activity and histone modifications such as acetylation that increases gene activity.

Precise definitions of epigenetics vary widely: from stable, heritable changes to very rapid, dynamic, transitory changes[19–21]. Most adult neuronal tissue is not mitotic. Therefore, it has been argued that heritable maintenance in the brain may be less of an issue than replication-independent methylation change and chromatin remodelling[22]. Many environmental factors, including nutrition, physiological and psychological stress, chemicals and infections, exert powerful influences on the epigenetic regulation of gene expression[23–28]. This, together with the realisation that epigenetic marks can be transmitted between generations, suggests that the boundary between environmental and heritable risks for disease is less distinct than recognised previously[29].

Epigenetic mechanisms regulate gene expression in physiological and pathological brain processes, and are an integral part of numerous brain functions[30]. They are plastic and reversible, suggesting a mechanism for environmental modulation of health and disease. Nutrition could be used throughout life to enhance mental well-being and alleviate the adverse effects of early-life experience. DNA methylation and histone modifications are of particular relevance to the current review because of important studies already undertaken on brain disorders and the role of nutrition in epigenetic modifications. These mechanisms are implicated in cognition, eating disorders, depression, autism and schizophrenia[25,31–33]. Studies on other epigenetic mechanisms involving RNA methylation, non-coding microRNA, telomere control and chromosomal position effects should also provide new understanding of mechanisms linking nutrition and brain health[23,34,35].

Genetic variability

Differences in DNA sequence can influence phenotype, responses to environment and risk of disease. Gene variants

https://doi.org/10.1017/S0029665112000237 Published online by Cambridge University Press

include relatively rare mutations, and more common SNP and copy number variants (CNV). These have the ability to markedly affect the extent to which nutrition influences gene expression.

Mutations involve a change in DNA sequence that can result in a loss or change in gene function. They are sometimes linked with rare single gene disorders, such as phenylketonuria. By contrast, common gene variants involving a change of a single nucleotide in at least 1% of the population are termed SNP. They have a key role in individual responses to nutrition and several investigations have highlighted their importance in neural and cognitive responses to energy status, specific nutrients and ageing[1,2,10,36]. SNP are linked with many polygenic common disorders: the combined action of alleles from several genes increases the risk of obesity, diabetes, cancers, CVD and brain disorders. Genome-wide association studies on very large numbers of individuals are significantly advancing understanding of the role of SNP in responses to nutrition. For example, a physically active life-style is associated with a 40% reduction in the genetic predisposition to obesity[37]. This finding resulted from genotyping twelve SNP in obesity-associated loci, in a study involving more than 20 000 people.

By contrast with SNP, CNV are structural gene variants that involve multiple copies or deletions of large parts of the genome, and can affect from 1 kb to many megabases of DNA per event[38]. CNV can be inherited or result from *de novo* mutation, and occur in genes, parts of genes and outside genes. Changes in a gene or its regulatory region can profoundly affect RNA and protein expression. These common insertions or deletions account for much of the genetic variability between people and are often linked with genes involved in molecular–environment interactions. Their precise role in multifactorial common diseases is the focus of considerable attention, with differences in methodologies sometimes accounting for false-positive associations[39]. The extent to which CNV are involved in neurodevelopmental and neuropsychiatric disorders is the subject of much current interest[40,41].

Mental health and well-being

Energy status and mental health

Good mental health is not simply the absence of mental health problems. Rather, it is characterised by positive advantages including the ability to learn, to interact with others and to cope with change and uncertainty[42]. Mental health has been defined as a state of well-being in which the person can realise their potential, cope with normal stresses of life, work productively and fruitfully and contribute to the community[43]. In recent years, considerable interest has been shown in the scientific study of well-being and happiness[44,45]. Cultural, economic, social and environmental factors such as nutrition all contribute to well-being and quality of life.

Energy status has a critical role in mental health and well-being. The term energy status is used here to include energy intake, physical activity and energy metabolism.

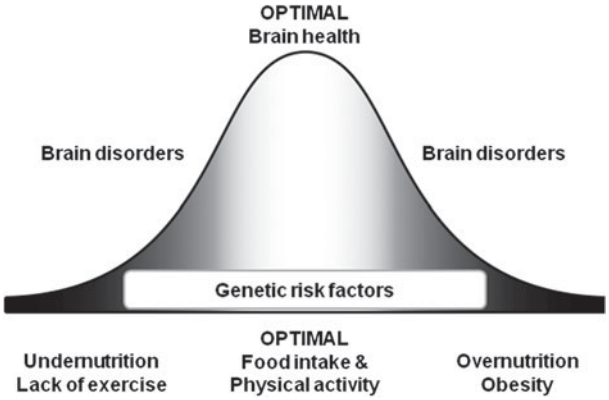

Fig. 2. Overview of the complex relation between energy status, genes and brain health. Optimal food intake and physical activity are linked with optimal mental health and well-being. The effects of energy intake are modified by specific dietary components e.g. DHA. Sub-optimal energy status, including undernutrition and overnutrition, is linked with mental and neurological disorders such as depression, schizophrenia, dementia and Alzheimer's disease. Incidence of these disorders is related to individual differences in genetic variability.

It thus has a broader and less precise meaning than energy balance. It is considered the more appropriate term in the present review because both overnutrition and undernutrition, for example, adversely affect brain health. Moreover, very few studies have focused on energy balance, genes and the brain. Rather, specific aspects of energy status have been investigated. Thus, studies on physical activity tend not to control energy intake, while those on energy intake do not usually control physical activity.

Considerable evidence links physical activity and optimal energy intake with improved mood and cognitive function, whereas both underweight and obesity are associated with impaired cognitive performance[1,2,46–48]. Studies on the psychotherapy eye movement desensitisation and reprocessing raise the possibility that outdoor activity such as walking may be especially beneficial for mental health and well-being. Although somewhat controversial, eye movement desensitisation and reprocessing is an effective and proven treatment for post-traumatic stress disorder and has also been used for treatment of depression[49]. Its unique element is a bilateral stimulation of the brain, such as eye movements, that may evoke neurological and physiological changes in treatment of adverse memories. These eye movements occur frequently when walking outdoors and may explain in part why such activity is especially beneficial.

Fig. 2 presents a working model of known interactions between energy status, genes and brain health. Rather than considering an individual as having high or low energy status, the focus is on optimal compared with sub-optimal energy status. Fig. 2 illustrates the complexity of the subject and the difficulties involved in understanding the interactions between nutrition, genes and the brain. Mechanisms underlying these interactions are discussed throughout the current review.

https://doi.org/10.1017/S0029665112000237 Published online by Cambridge University Press

Underlying mechanisms: signalling molecules and epigenetics

Energy status throughout the life-cycle influences numerous hormones and growth factors[50,51]. These act as nutritional sensors to influence brain structure and function via changes in gene expression. Molecules such as glucocorticoids, thyroid hormones, insulin, insulin-like growth factors and brain-derived neurotrophic factor (BDNF) are involved in multiple cell-signalling systems and neural networks that mediate the actions of energy on brain health[1,2,24,52].

Recent advances in elucidating the role of BDNF in neurological and mental health disorders are especially important[53]. This molecule is involved in prenatal and adult neurogenesis, in the growth, differentiation and survival of neurons and synapses, and in synaptic plasticity. BDNF has a critical role in the cerebral cortex and hippocampus and is vital for learning, memory and cognition. The beneficial effects of physical activity on mental health and cognition can be explained in part by induction of BDNF gene expression in the hippocampus[52,54]. Moreover, the adverse effects of high energy intake or strenuous exercise are related to an increase in reactive oxygen species, decrease in BDNF expression and compromised synaptic plasticity and cognition.

Bioenergetics provides the interface between the environment and the epigenome, and there is a close relation between energy metabolism and epigenetic events[55,56]. Recent findings show that exercise influences BDNF-induced brain plasticity in the hippocampus via epigenetic remodelling of chromatin containing the BDNF gene[57]. Voluntary wheel-running in rats reduces DNA methylation and affects histone acetylation in the BDNF exon IV promoter, a region of the gene that is highly responsive to neuronal activity. These changes are associated with concomitant increases in BDNF mRNA and protein expression. In these studies, animals were fed *ad libitum*, suggesting that changes in energy intake associated with exercise may also affect BDNF expression. Specific nutrients can add to the positive effects of exercise on the brain. The *n*-3 PUFA DHA enhances the effects of exercise on BDNF-related synaptic plasticity and cognition[58].

Taken together, current evidence suggests that optimal energy status enhances mental health and well-being in part via changes in mitochondrial energy metabolism, epigenetic regulation of the BDNF gene and synaptic plasticity. Many other signalling molecules are involved[50–52]. For example, insulin-like growth factor-1 mediates the actions of BDNF, and the histone deacetylase sirtuin silent information regulator 1 is modified by energy metabolism. Glucocorticoids, thyroid hormones and other ligands of the nuclear receptor super-family may also play a pivotal role. Their receptors act as transcription factors to affect multiple genes via epigenetic changes involving histone acetylation and chromatin remodelling[50,58].

Gene variability: brain-derived neurotrophic factor

Gene variants of multiple signalling molecules may alter their responsiveness to changes in energy intake and physical activity. A common variant of the BDNF gene is the SNP Val66Met. This polymorphism is related to abnormal trafficking and secretion of BDNF in neurons, and is associated with abnormal functioning of the hippocampus and memory processing[59]. There is considerable interest in whether this SNP is linked with hippocampal atrophy and age-related memory impairment[54]. Current data suggest only a weak association, and this may reflect complex interactions with other genes and environmental factors.

Genetic studies have revealed consistent associations between individual variability in the BDNF gene, blood levels of BDNF and incidence of eating disorders[60]. The SNP-270C/T is linked with bulimia, while Val66Met is associated with both anorexia and bulimia. This raises the possibility that the effects of energy status on mental health and well-being are significantly affected by variations in multiple genes that code for signalling molecules involved in brain development and function.

Mental disorders: schizophrenia

Nutrition, genes and mental disorders

Disorders of mental health affect approximately 25% of the population each year. Common disorders such as depression, anxiety disorders and cognitive dysfunction affect one in ten people. Less common problems such as schizophrenia and bipolar disorder affect one in 100. There is a wide spectrum in severity of mental disorders and a threshold after which mental symptoms become a diagnosis. Thus, it can be difficult to define the point at which normal worry becomes depression-anxiety as a mental disorder. The precise role of nutrition in mental disorders has yet to be established. However, a high-energy diet, sedentary lifestyle, obesity and diabetes are linked with risk of depression and dementia, while prenatal undernutrition is linked with many mental disorders in later life[1,2].

Advances are being made in understanding the genetic basis of many mental health problems, and the role of gene–environment interactions and epigenetic factors in these disorders[61–63]. The neurotrophic hypothesis suggests that stress reduces the activity of neurotrophins such as BDNF, resulting in decreased hippocampal function and ultimately depression. Considerable research in animal models also shows that the antidepressive effect of exercise is correlated with increased levels of BDNF protein[64]. Moreover, the Val66Met SNP in the BDNF gene results in reduced intracellular trafficking and secretion of BDNF protein, and is associated with increased depression. CNV also have a role in mental disorders. Especially important is the recent finding of deletions and duplications in the chromosomal region 16p11.2 in major depressive disorder, since this region is linked with other neuropsychiatric disorders[65,66]. Moreover, experimental studies suggest that gender differences in epigenetic mechanisms may underlie risk and resilience for developing neurological and mental health disorders[67].

Schizophrenia: symptoms, incidence and causes

Schizophrenia is a severe mental disorder with symptoms that include profound disruptions in thinking, hallucinations

https://doi.org/10.1017/S0029665112000237 Published online by Cambridge University Press

and delusions, and social and emotional dysfunction[68]. Some twenty-four million people are affected worldwide and, by contrast with late-onset Alzheimer's, the peak age of onset is only 20–28 years in men and 26–32 years in women. Substantial costs are associated with schizophrenia. At the personal level, there is frequently unemployment, poverty and homelessness. Life expectancy is reduced by 12–15 years because of the sedentary lifestyle, obesity, smoking and suicide. Economically, it is estimated that in the USA, for example, costs associated with schizophrenia are greater than for all cancers combined.

Causes of schizophrenia are multifactorial and involve genetics and environment[69–71]. There is a 10% chance of developing schizophrenia if a first degree relative such as a sibling or parent is affected. However, 50% of cases are sporadic, with no family member being affected. Progress is being made in schizophrenia genomics and current debate focuses on the relative importance of rare mutations that confer high disease susceptibility, compared with multiple common variants that each have small effects on disease risk[72,73]. There is considerable genetic heterogeneity in this complex brain disorder and it is often linked with other neurodevelopmental problems such as autism or bipolar disorder, suggesting that it should not be treated as a single disease. Molecular aetiology rather than clinical symptoms may therefore provide the basis for future diagnosis and treatment.

SNP and CNV are implicated in neuropsychiatric disorders such as intellectual disability, autism and schizophrenia[41,74,75]. Analysis of the role of CNV in disease is extremely complex[39] and, assuming these findings on CNV and schizophrenia are methodologically sound, they suggest an important role not only for single base changes but also for gene dosage in this disorder. Increasing evidence links genomic and epigenomic instability, and multiple fragile site regions of the genome, to schizophrenia and autism[70]. Genomic instability refers to an increased mutation rate involving chromosomal abnormalities, translocations, insertions, deletions and base changes. Epigenomic instability refers to perturbed responses of gene regulation to environmental fluctuations. This suggests that energy status may exert a critical influence on the development of schizophrenia, via interactions with multiple gene variants and epigenetic processes.

Many environmental factors have been linked with schizophrenia including diet, place and time of birth, infections, obstetric factors, prenatal and psychosocial stress, chemicals, drugs and paternal age[69,76]. Considerable evidence shows that epigenetic mechanisms are involved in the pathogenesis of schizophrenia[31], reinforcing the suggestion that it is, in part, a neurodevelopmental disorder. This indicates a key role for early-life nutrition in schizophrenia and highlights the potential for novel developments in its prevention.

Prenatal nutrition and schizophrenia

Two historically significant events have provided new understanding of the causes of schizophrenia: the Dutch Hunger Winter of 1944–1945, and the Great Leap Forward and subsequent Chinese Famine in 1959–1961. Several studies have shown a clear link between prenatal exposure to famine and schizophrenia[77–79]. In Wuhu Prefecture, Anhul, China, evaluation of birth rates in 1956–1964 and psychiatric records between 1971 and 2001 indicates a 2-fold increase in risk of adult schizophrenia in those exposed to severe prenatal undernutrition. The risk is related to the severity of the famine and is greatest when exposure to famine occurs around conception or early gestation.

Several hypotheses can be postulated to link prenatal famine exposure with schizophrenia. These include preconceptual effects on sperm, and the possibility that schizophrenia risk alleles may confer an advantage in times of famine. However, especially significant is the hypothesis that epigenetic mechanisms are involved. Key genes in brain development may be altered by prenatal nutritional deficiencies in energy, protein, carbohydrate, micronutrients such as iodine, Cu and Zn, and vitamins such as the B-complex and folic acid.

Persistent epigenetic changes are linked with prenatal exposure to famine[80,81]. The focus of these studies was loci linked with growth and metabolic diseases. Periconceptual exposure to the Dutch famine is associated with long-term epigenetic differences: in blood from adults aged approximately 58 years, DNA methylation patterns of genes such as *IL10* and *INSIGF* were markedly different from those in unexposed same-sex siblings. In the future, it may be possible to establish whether prenatal famine exposure is also linked with epigenetic changes in key neurodevelopmental genes. Such changes could affect gene expression and brain function, with specific effects being related to stage of development.

Intrauterine growth restriction and programming of brain health

Recent advances in elucidating mechanisms underlying the programming of adult health and disease are clarifying the role of early malnutrition in later brain health. Intrauterine growth restriction (IUGR) is a naturally occurring form of prenatal undernutrition, with several different causes, that reflects a reduction in nutrient supply to the fetus. Infants born small-for-gestational age, especially when they are also preterm, are at major risk of impaired neurodevelopment, multiple cognitive deficits, mental health problems and schizophrenia in later life[1,2,82–84].

Findings on epigenetic changes induced by prenatal famine exposure[81] raise the possibility that similar changes are induced by IUGR. However, recent studies demonstrate that this is not necessarily the case: in whole blood from 19-year-olds, growth restriction early in development was found not to be associated with DNA methylation at loci affected by prenatal famine exposure[85]. These differences may be due in part to the stage of prenatal development at which the nutritional insult occurred. Moreover, these two studies were undertaken in adults of very different age. Investigations in the IUGR and famine studies were undertaken in individuals aged approximately 19 and 58 years, respectively, and this may have affected the mechanisms by which gene expression was regulated. Recent animal studies have shown that the

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effects of maternal diet on gene expression of the offspring operate through distinct age-dependent regulatory mechanisms[86]. In young animals, effects of diet on myostatin, a member of the transforming growth factor β family, were mediated by changes in CCAAT/enhancer-binding protein binding without epigenetic modifications. However, in older animals changes in both CCAAT/enhancer-binding protein and epigenetic marks such as histone modifications and microRNA expression were observed. Taken together, these studies on prenatal undernutrition lead to the important conclusion that epigenetic or non-epigenetic changes may result in similar health outcomes.

Impairments of BDNF and its receptor tropomyosin-related kinase receptor type B are implicated in the pathogenesis of schizophrenia and depression[53]. Experimental findings suggest mechanisms by which prenatal undernutrition is linked with schizophrenia. In cultured cortical neurons from a rat model of IUGR, tropomyosin-related kinase receptor type B is down-regulated, as are downstream intracellular signalling pathways[87]. This suggests that IUGR results in reductions in cell viability and synaptic function, and associated changes in clinical symptoms of schizophrenia. Future investigations should help to elucidate the mechanisms which link early undernutrition to schizophrenia, and suggest possible preventative approaches to this devastating disorder. Public health interventions related to prenatal nutrition and individual variability in key susceptibility genes may be especially beneficial.

Neurological disorders: Alzheimer's disease

Disorders of neurodevelopment and neurodegeneration

Neurological disorders can be classified as neurodevelopmental, e.g. eating disorders, autism and schizophrenia, or neurodegenerative, e.g. cognitive decline, dementia and Alzheimer's disease. However, it is becoming increasingly recognised that the distinctions between these two categories are not always clear cut. Aspects of Alzheimer's may originate in early-life[88,89], and schizophrenia has been considered as both neurodevelopmental and an ageing disorder[90]. This is not surprising when it is appreciated that early-life experiences have both immediate and long-term effects on brain development and function[83,84,91,92]. Progress is being made in understanding the molecular basis of normal ageing and Alzheimer's, and the role of nutrition–gene interactions in these conditions[8,93,94].

Alzheimer's: symptoms, incidence and causes

Alzheimer's disease is a progressive neurodegenerative disorder involving brain shrinkage, up to 60% loss of neurons, and loss of brain function. In its most common late onset form, there is no discrete neuropathology[95]. Instead, there is a wide range of clinical symptoms representing a gradual accumulation of multiple pathologies due to multiple risk factors over the life course. These include loss of memory and language, confusion, irritability, aggression, mood change, dementia and loss of physiological function. The realisation that Alzheimer's is a diffuse clinical syndrome highlights the difficulties involved in optimising its prevention and treatment.

The economic and human costs of this disorder are immense. In the UK more than 800 000 people have dementia and annual costs are approximately £23 billion. The worldwide cost in 2010 was US$604 billion, and for the sufferer, family and friends there are considerable personal, emotional, social and financial costs. In 90–95% of cases the age of onset is over 65 years, and average life expectancy is 8 years with a range of 4–20 years. Concomitant with increasing life-span, the worldwide incidence of Alzheimer's is increasing: 35·6 million people were affected in 2010, and it is estimated that this will reach 115·4 million in 2050[96,97].

Causes of Alzheimer's are multifactorial and complex, involving many genetic and environmental factors[36,88,89,98]. There are changes in expression of thousands of genes, and up-regulation of multiple pathogenic pathways including amyloid β-peptide deposition, tau hyperphosphorylation, apoptosis or cell death, inflammation, oxidative stress and energy metabolism.

Alzheimer's is mainly sporadic, in that the late-onset form does not involve inherited mutations. Multiple common gene variants are implicated as risk factors. Of particular relevance is apoE, which is essential for cholesterol trafficking in the central nervous system. It has a critical role in Alzheimer's: just one copy of the gene variant apoE4 is linked with a 4-fold increase in disease risk, while two copies increase the risk 10-fold. By contrast, the apoE2 variant may protect against Alzheimer's, relative to the common apoE3 allele. Genome-wide association studies are now identifying SNP in numerous candidate genes that may also have important roles in Alzheimer's[98]. Many of these are involved in inflammation and metabolic disruptions associated with the disease. Ongoing studies by the International Genomics of Alzheimer's Project involve 10 million SNP and should provide further understanding into causes of the disease. They will also open the possibility of detailed investigations on nutrition–gene interactions in the prevention and amelioration of this debilitating brain disorder.

Energy status and Alzheimer's

Several comprehensive reviews on Alzheimer's and nutrition highlight the importance of diet and specific nutrients in the cause of the disease[5,99,100]. Of particular interest in the present context is the extent to which energy status can help prevent or treat the symptoms of Alzheimer's. Physical activity has beneficial effects, and aerobic exercise can increase brain volume and improve cognitive function in older adults. Especially important are recent findings that specific brain regions are affected selectively. MRI showed that after 1 year of aerobic exercise, involving walking for three 40 min sessions per week, the anterior hippocampus increased in size and the normal loss of hippocampal volume in late adulthood was prevented[101]. Moreover, these changes were associated with increased serum BDNF and improved memory function. These findings are especially relevant because brain shrinkage can predict cognitive decline in otherwise healthy adults[102]. Structural brain changes occur many years before clinical cognitive

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https://doi.org/10.1017/S0029665112000237 Published online by Cambridge University Press

decline and are localised to regions affected by Alzheimer's neuropathology. No data on food intake were available for this study[101] but it is probable that level of energy intake can also affect brain volume. This will be an especially valuable area for future investigation.

Traditionally, studies on cognitive decline with age focus on people aged over 60 years. However, striking findings from a recent study in over 7000 people showed that cognitive decline is already evident in middle age, at 45–49 years[103]. This is especially significant when it is realised that modest differences in cognitive performance in earlier life predict larger differences in risk of dementia and Alzheimer's disease in later life[104]. In view of the beneficial effects of physical activity on the BDNF gene and brain health, it is probable that both moderate aerobic exercise and relatively low levels of activity such as walking and gardening are beneficial in preventing and alleviating Alzheimer's. In this context, definitions of optimal energy intake throughout the life-cycle need to be established.

Not only is nutrition implicated in the cause of Alzheimer's but nutritional problems arise as a consequence of the disorder. These are associated with the physical and mental decline which makes patients less able to cope and care for themselves. Recent findings suggest that 86% of patients with advanced dementia have eating problems[105]. These include reduced oral intake, refusal to eat or drink, problems with chewing and swallowing, and resultant dehydration and weight loss. Together with mobility problems, the overall negative impact of Alzheimer's on optimal energy status can therefore be significant.

Depending on the severity of the symptoms, a dual approach for optimal nutrition in the treatment of patients with Alzheimer's is suggested. When possible, physical activity should be encouraged. If food intake is adequate, then the focus should be on a balanced diet of energy and nutrients. If food intake cannot be optimised, attempts should be made to improve food intake, focusing on especially beneficial nutrients such as *n*-3 fatty acids, including DHA, and the ratio *n*-3:*n*-6 fatty acids. Recent findings also suggest a key role for B vitamins and folate in reducing homocysteine, a risk factor for brain atrophy and dementia[106]. In people aged over 70 years, B vitamin supplements for 2 years slowed cognitive and clinical decline in those with mild cognitive impairment who also had elevated baseline homocysteine levels. By contrast, excess carbohydrates such as fructose should be avoided, especially if there is a relative deficiency of fats and cholesterol[100].

Brain energy metabolism, ageing and Alzheimer's

Recent findings on changes in brain energy metabolism during ageing and in Alzheimer's are increasing understanding of mechanisms underlying cognitive decline and dementia[107,108]. Evidence from clinical and experimental models suggests that brain hypometabolism may precede and therefore contribute to the neuropathology that causes clinical symptoms of the disease. Lower brain glucose metabolism occurs before the onset of cognitive decline in carriers of apoE4 and in those with a maternal history of Alzheimer's. This hypometabolism may be due to defects in brain glucose transport, disrupted glycolysis and impaired mitochondrial function.

These studies suggest that future strategies to reduce the risk of Alzheimer's could involve improvement of insulin sensitivity by sustained improvement of brain and systemic glucose metabolism. Moreover, brain hypometabolism may affect glucose more than ketones, suggesting that strategies could also include the replacement of glucose by ketones as an alternative physiological fuel[108]. The hippocampus is especially vulnerable to reduced energy supply, and optimisation of brain energy metabolism with ketogenic supplements could help reduce further cognitive decline.

An important nutritional component that affects brain energy metabolism is the *n*-3 fatty acid DHA. Dietary supplements increase GLUT1 expression in rat brain cells, and DHA levels in brain cell membranes are positively correlated with GLUT expression[109]. A low dietary intake of DHA and low DHA levels in the hippocampus may contribute to cognitive decline in Alzheimer's[110], and this may be due in part to the role of DHA in brain glucose transport. Of additional importance is the knowledge that the cognitive benefits to be gained from DHA supplementation are related to apoE genotype[99]. This helps explain the inconsistent results in human intervention studies with DHA and suggests that supplementation should be targeted according to genotype.

Gene variants confer advantages and disadvantages

Health outcomes resulting from improved nutrition aimed at preventing or treating Alzheimer's are extremely difficult to predict. They are related in part to individual differences in multiple gene variants involved in the response. Such variants can have both positive and negative effects, and precise outcomes are dependent on age and environment.

It is well-recognised that the apoE4 genotype is linked with cognitive decline and Alzheimer's in adults. This may be due in part to greater vulnerability to environmental factors because of poor brain protection and repair mechanisms. Nevertheless, apoE4 carriers sometimes have a lower level of risk factors for cognition and dementia such as inflammation, hyperhomocysteinemia and overweight[99]. Moreover, this genotype can have a protective role in the cognitive development of young children living with the environmental stresses of malnutrition and infection[111]. Findings in shanty town children in North East Brazil show that apoE4 is relatively common and has a protective role in the cognitive development of those with recurrent and persistent episodes of diarrhoea. The probability is that the apoE4 genotype confers an evolutionary advantage because it increases cholesterol, a critical factor for optimal neurodevelopment, and protects against infection and malnutrition.

Epigenetic mechanisms are implicated in Alzheimer's

Recent studies have highlighted the importance of epigenetic mechanisms in Alzheimer's, confirming that environmental factors play a key role in this disorder.

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Indeed, it has been postulated that epigenetic mechanisms may provide a unique integrative framework for the pathologic diversity and complexity of Alzheimer's[88].

Considerable evidence demonstrates distinct epigenetic changes in the brains of Alzheimer's patients, and in animal and cell culture models of the disease. These include changes in DNA methylation, histone modifications, non-coding microRNA and mRNA expression[29,88,112]. The patterns of change are often complex with epigenetic modifications occurring at multiple loci. Nevertheless, results from a genome-wide study clearly indicate decreases in DNA methylation markers in cortical neurons from Alzheimer's patients compared with elderly controls, whereas there are no such changes in cerebellum, a region that is relatively spared in Alzheimer's[88].

The extent to which epigenetic changes in Alzheimer's and in normal ageing are linked with nutrition is the subject of much current investigation. Specific nutrients such as folate, Met and homocysteine are closely linked with DNA methylation mechanisms. The probability is that energy status throughout the life-cycle can markedly influence epigenetic marks in the brain, with concomitant effects on a wide range of neurological conditions including dementia. Important new studies in animal models are determining the roles of dietary restriction and specific nutrients in modulating brain ageing via epigenetic processes, at different stages of the life-cycle (JC Mathers, unpublished results). The results of these studies, together with proposed investigations in human subjects, will provide new insights into optimal nutrition for brain health and risk of degenerative disease throughout life.

Conclusions

The current review highlights recent progress in understanding mechanisms by which nutrition–gene interactions influence brain health throughout the life-cycle. Critical analysis of numerous clinical and experimental investigations reveals that energy status, i.e. energy intake, physical activity and energy metabolism, has major influences on the brain. Physical activity and optimal energy intake improve mental health and well-being, whereas undernutrition, overnutrition and obesity are implicated in disorders of mental health and neurology such as depression, schizophrenia and Alzheimer's. The overall impact of energy status is related to age and stage of development, interactions with other dietary components, and individual gene variability in SNP and CNV. It is clear that optimal food intake and optimal physical activity are essential for brain health, and that multiple genes are involved in this response. However, the precise definition of 'optimal' is extremely difficult and will undoubtedly be the subject of future investigations.

The effects of energy intake and physical activity on gene expression are modulated by specific nutrients such as the *n*-3 fatty acid DHA. Numerous signalling molecules including BDNF, tropomyosin-related kinase receptor type B, insulin-like growth factors and nuclear hormone receptors play a critical role in mediating the actions of energy intake, activity and energy metabolism on the brain. Differences in individual responses can be explained in part by multiple gene variants involved in cell signalling and neural networks. Future studies on BDNF, apoE and millions of other gene variants should suggest new possibilities for optimisation of mental health and well-being, and the prevention and treatment of brain disorders. Progress in new technologies, including genomics and epigenomics, is advancing understanding of the links between nutrition, genes and the brain. Epigenetic mechanisms involving DNA methylation, histone acetylation and microRNA mediate many of the actions of nutrition on gene expression and suggest future possibilities for prevention and treatment of brain disorders.

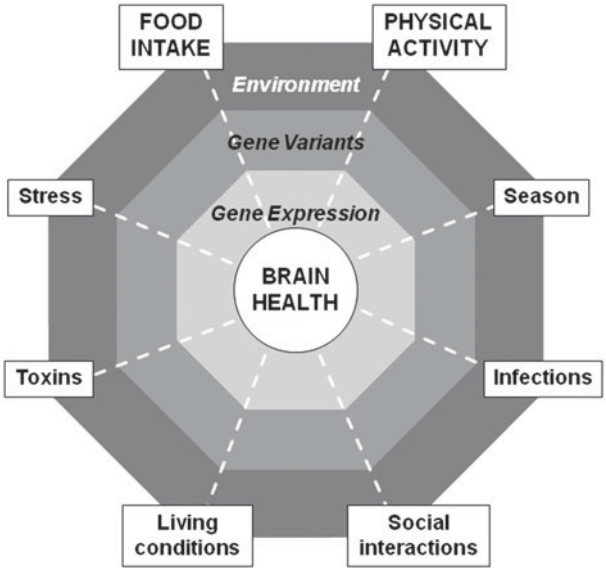

Fig. 3. Environment–gene interactions and brain health. Numerous environmental variables have major actions on brain health. These actions are mediated by changes in gene expression and are dependent on multiple gene variables. The impact of environmental factors on mental health, and neurodevelopmental and neurodegenerative disorders is related to gender and stage of life cycle. Outcome is related to life-experience and the complex network of interactions between environmental factors.

Nutrition is only one of many environmental factors that influence brain health, with outcome being dependent on age, gender and life experience. Fig. 3 shows that, together with numerous genetic factors, they comprise a sophisticated control network with a major impact on brain health. Future investigations will benefit from the novel methodologies of systems biology, to increase understanding of the complex interplay between these factors in determining optimal brain health throughout life. In the longer-term, this complex but holistic approach should enable targeted recommendations to be made for optimising mental health and well-being in society, and reducing common mental disorders such as depression and anxiety. Future research should also enable significant advances in the prevention, treatment and alleviation of devastating mental and neurological disorders such as schizophrenia and Alzheimer's.

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https://doi.org/10.1017/S0029665112000237 Published online by Cambridge University Press

Acknowledgements

I thank many colleagues for expert advice and valuable discussion, especially J. C. Mathers, Director of Human Nutrition Research Centre, Institute for Ageing and Health, Newcastle University, and G. C. M. Selby, Ministry of Justice Mental Health Review Tribunal. I thank the organisers, especially C. Agostini and S. Agostini, for inviting me to participate in Mega Evento Nutrição 2011. M. J. D. is a Fellow of Wolfson College, University of Cambridge and thanks the library and computing staff of the College and the University for expert advice. The author declares no conflicts of interest.

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