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NUTRITION, GENES, AND NEUROSCIENCE: IMPLICATIONS FOR DEVELOPMENT, HEALTH, AND DISEASE

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1.1 INTRODUCTION

Nutrition–gene interactions play a pivotal role in cognitive function and neurological disease throughout life. Nutrition is one of many environmental factors that profoundly alter the phenotypic expression of a given genotype, with major implications for development, metabolism, health, and disease [1–4]. These effects are mediated by changes in expression of multiple genes and can involve epigenetic mechanisms: nutrition is one of many epigenetic regulators that modify gene expression without changes in DNA sequence. Responses to nutrition are in turn affected by individual genetic variability. The effects of nutrition on gene expression are exerted throughout the life cycle, with prenatal and early postnatal life being especially critical periods for optimal development. Changes in gene expression may be dynamic and short term, stable and long term, and even heritable between cell divisions and across generations.

This review focuses on the following key topics. First, a short overview is provided on the role of nutrition in cognitive neuroscience. Second, mechanisms underlying nutrition–gene interactions are discussed, especially in relation to the roles of epigenetics and genetic variability in neuroscience. Third, attention is focused on the importance of environment and epigenetics in neurological health and disease. Finally, the role of early nutrition in brain development and later neurological disease is addressed. Overall, this review highlights the critical importance of nutrition–gene interactions to optimal neurological function and prevention and treatment of multiple neurological disorders.

1.2 NUTRITION AND COGNITIVE NEUROSCIENCE

The role of nutrition in cognitive neuroscience is highly complex because, as with all aspects of nutrition, it is multifactorial. It is not concerned simply with the impact of a single chemical on the brain but with numerous interactions between multiple nutrients, metabolites, food, and other environmental and genetic factors. Nevertheless, considerable evidence now links many aspects of nutrition with cognition, mental health and well-being, neurological dysfunction, and disease [1–9]. Protective roles are suggested for the Mediterranean diet, optimal energy status, fish, fruits, vegetables, polyphenols, omega-3 polyunsaturated fatty acids, iron, zinc, copper, and numerous vitamins.

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There are many inconsistencies between studies, in part because of methodological differences associated with the multifactorial nature of the subject. However, taken together, strong evidence clearly links optimal energy status and the Mediterranean diet with optimal cognitive function and prevention of cognitive decline and neurological dysfunction.

1.2.1 Specific Nutrients

Clearly, it is difficult to assess the precise benefits of specific nutrients on neurological and cognitive function. Nevertheless, significant links have been reported in studies on many nutrients including long-chain polyunsaturated fatty acids, vitamins A–E, and trace elements [1, 4, 8, 10–16]. Interactions and synergism between specific nutrients are especially important and may help in part to explain inconsistencies between studies and the importance of an optimal balanced diet.

Despite some controversy, substantial evidence suggests a vital role of omega-3 polyunsaturated fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in neurodevelopment, cognition, mental health, and neurodegeneration. They enhance memory, mood, and behavior and reduce depression. By contrast, deficiency of omega-3 fatty acids is linked with increased risk of attention-deficit/hyperactivity disorder, depression, dementia, Alzheimer's disease, and schizophrenia. Moreover, diets high in trans and saturated fats adversely affect cognitive function. The balance between omega-3 and omega-6 fatty acid intakes may be especially critical for optimal mental health. Competitive inhibition occurs between these two groups of fatty acids, and Western diets low in omega-3 and high in omega-6 may contribute to reduced accretion of DHA, inhibition of secondary neurite growth, and impaired brain development and function.

Trace elements including copper, zinc, and iron are important in neurodevelopment, neurotransmitter synthesis, and energy metabolism and have key roles in cognition. Low plasma copper is linked with cognitive decline, and zinc deficiency is linked with attention-deficit/hyperactivity disorder in children; impaired memory and learning in adolescents; and stress, depression, and cognitive decline in adults. There is a fine balance between the beneficial and harmful effects of many trace elements, and interactions between trace elements are important for optimal brain function. These may be especially important during critical stages of development and periods of vulnerability to neurological diseases.

1.2.2 Mediterranean Diet

It is increasingly apparent that the overall balance of specific nutrients and foods in the diet is important for optimal function. In relation to cognition and prevention of neurological disorders, a protective role has been reported for fish, fruit, and vegetables. Considerable attention is now focused on defining an optimal balanced diet, and future studies should improve understanding of optimal nutrition throughout the life course. In this context, the traditional Mediterranean diet is regarded as especially beneficial [17, 18]. It is characterized 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. Higher adherence to this diet may contribute to the prevention of several brain disorders including depression, cognitive impairment, Alzheimer's disease, and Parkinson's disease. However, it is also apparent that suboptimal energy status and overnutrition, even of an optimal Mediterranean diet, are not beneficial to neurological function, and the importance of energy status is therefore discussed in Section 1.2.3.

1.2.3 Energy Status

Many studies link energy status with cognitive function and neurological disorders. The term energy status is used here to include energy intake, physical activity, energy metabolism, and related changes in body composition. It is a broader and less precise term than energy balance and reflects the multifaceted influence of this critical component of nutrition. Moreover, in some studies, it can be difficult to determine whether effects on brain function are due to changes in energy intake and/or energy expenditure: studies on physical activity do not always control energy intake, while those on energy intake do not always control physical activity.

The interactions between energy status and cognition are multifactorial and complex. Nevertheless, evidence highlights close links between energy status and mental health [1, 4, 19, 20]. Physical activity is beneficial to mental health and

well-being: it decreases the risk of depression and improves mood and self-esteem. Regular aerobic exercise increases brain volume and reduces the risk of cognitive impairment, dementia, and Alzheimer's disease in older adults. Undernutrition, without malnutrition, reduces age-related deficits in cognitive function, whereas overnutrition can result in cognitive dysfunction.

High-energy diets and a sedentary lifestyle are leading to increased prevalence of obesity and diabetes. There is a link between these conditions and risk of impaired cognitive function, depression, and dementia that is age related [21, 22]: obesity in midlife years 40–50s is linked with increased dementia, whereas by the late 70s the risk has inverted and obesity may even be protective of dementia. Moreover, patients with severe mental illness such as schizophrenia are at greater risk of metabolic syndrome and associated obesity, type 2 diabetes, and dyslipidemia [23]. Mechanisms involving chronic inflammation, cell signaling pathways, metabolic dysfunction, and genetic factors also link overnutrition with numerous disorders including Alzheimer's disease [24]. Indeed, Alzheimer's can be regarded as a neuroendocrine degenerative disorder that has elements of both insulin/insulin-like growth factor (IGF) resistance and insulin deficiency, suggesting that it be referred to as "type 3 diabetes" [25].

1.3 MECHANISMS UNDERLYING NUTRITION–GENE INTERACTIONS

Nutrition affects neurological function and cognition via numerous influences on cell membranes, enzymes, neurotransmitters, metabolism, neurogenesis, and synaptic plasticity. Many of these diverse effects are mediated by expression of multiple genes and associated regulatory networks. An additional layer of complexity is provided by individual genetic variability: the differences in protein-coding and noncoding regions of the genome have major influences on individual response to nutrition.

The term "nutritional genomics" is often used interchangeably with "nutrigenomics" and involves the study of nutrition–gene interactions. This includes both the effects of nutrition on gene expression ("nutrigenomics") and the effects of genetic variability on responses to nutrition ("nutrigenetics") [2, 26, 27]. Figure 1.1 outlines key mechanisms involved in nutrition–gene interactions.

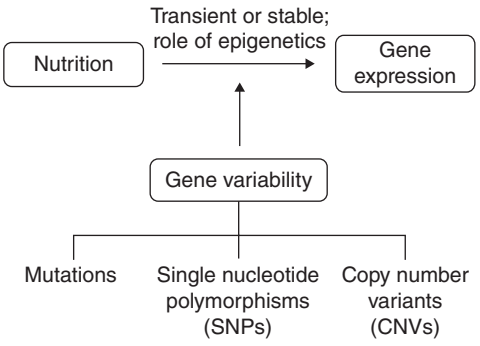

Fig. 1.1 Overview of nutrition–gene interactions. Modified from Dauncey, M.J. Recent advances in nutrition, genes and brain health. *Proceedings of the Nutrition Society* 2012, 71, 581–591.

1.3.1 Nutritional Regulation of Gene Expression

Considerable progress is to be made in understanding the molecular mechanisms and neural pathways underlying the effects of nutrition on gene expression [2, 4, 6, 24, 28, 29]. Cellular and nuclear receptors play a key role in mediating the effects of nutrition on numerous genes involved in neural function and brain plasticity.

Nutrition has both direct and indirect effects on gene expression, with the latter being exerted via cell signaling pathways. In relation to direct effects, many nutrients and metabolites are ligands for nuclear receptors/transcription factors, for example, vitamin A (retinoic acid receptor, RAR), vitamin D (vitamin D receptor, VDR), vitamin E (pregnane X receptor, PXR), calcium (calcineurin), zinc (metal-responsive transcription factor 1, MTF1), and fatty acids (peroxisome proliferator-activated receptors, PPARs; sterol regulatory element-binding proteins, SREBPs).

In relation to indirect effects, energy status influences numerous hormones and growth factors that act as nutritional sensors to influence the brain via changes in gene expression. Polypeptide hormones including growth hormone, IGFs, insulin, and brain-derived neurotrophic factor (BDNF) act on plasma membrane-bound receptors to trigger gene transcription via intracellular signaling pathways. Lipophilic hormones, including thyroid hormones and glucocorticoids, act on their nuclear receptors to regulate the expression of transcription of multiple genes via DNA binding and chromatin remodeling. Epigenetic mechanisms are involved in many of these responses, and these are discussed in the next section.

1.3.2 Epigenetics: Definition and Mechanisms

Nutrition affects gene expression at levels of transcription, translation, and posttranslational modifications, and epigenetic mechanisms play a key role in some of these responses. These link nutrition with outcome in relation to health or disease. Many factors act as powerful influences on the epigenetic regulation of gene expression, including nutrition, age, gender, physiological and psychological stress, chemicals, and infections. Thus, the epigenome provides a critical layer of regulation: nutrition is one of many epigenetic regulators that can modify gene expression and hence phenotypic expression [3, 4, 30].

The term epigenetics means "above genetics" and includes mechanisms that alter gene expression without changes in DNA sequence. Precise definitions vary widely: investigations may be concerned with transient or stable effects, with the latter sometimes involving heritable changes between generations. Epigenetic mechanisms often involve chemical marking of chromatin, that is, the form in which DNA is packaged with histone proteins in the cell nucleus. Epigenetic marks can induce chromatin remodeling and related changes in gene expression. They include DNA methylation, which reduces gene activity, and histone modifications such as acetylation, which increases gene activity.

Additional epigenetic mechanisms involve non-protein-coding RNAs (ncRNAs), RNA editing, telomere control, and chromosomal position effects. Although protein-coding genes are the subject of many functional studies, most of the genome gives rise to ncRNAs that play key roles in development, health, and disease [3, 31–33]. Detailed investigations have revealed a central role for ncRNAs as regulators of transcription, epigenetic processes, and gene silencing. Moreover, there are key interactions between ncRNAs and environmental factors, such as nutrition [3, 34, 35]. Multiple gene variants in protein-coding and noncoding regions of the genome add a further level of control.

1.3.3 Gene Variability and Individual Responses to Nutrition

Individual differences in gene variability can affect gene expression, phenotype, responses to environment, and risk of neurological disorders [2, 3, 27, 36]. Gene variants include mutations, single nucleotide polymorphisms (SNPs), and copy number variants (CNVs). These have the ability to markedly affect the extent to which nutrition influences gene expression.

Mutations involve a change in DNA sequence that may result in a loss or change in gene function. They can be 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 SNPs. They have a key role in individual responses to nutrition and are linked with many polygenic common disorders in humans: the combined action of alleles from several genes increases the risk of obesity, diabetes, cancers, cardiovascular disease, and neurological disorders.

Genome-wide association studies (GWAS) on large numbers of individuals are significantly advancing understanding of the role of SNPs in responses to nutrition. For example, a physically active lifestyle is associated with a 40% reduction in the genetic predisposition to obesity [37]. This finding resulted from genotyping 12 SNPs in obesity-associated loci, in a study involving more than 20,000 people. Of additional significance are findings from a recent GWAS of metabolic traits that reveals novel links between gene, metabolites, and disease [38].

Common gene variants such as SNPs also affect epigenetic mechanisms and hence individual responses to nutrition and susceptibility to disease. A study of genetic and nongenetic influences during pregnancy on infant global and site-specific DNA methylation highlights important roles for folate gene variants and vitamin B12 status of infants and mothers [39].

By contrast with SNPs, CNVs are structural gene variants that involve multiple copies or deletions of large parts of the genome. They are either inherited or resulted from *de novo* mutation; occur in genes, parts of genes, and outside genes; and thus 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 molecule–environment interactions. The extent to which CNVs are involved in neurological disorders is the subject of considerable interest [40, 41].

1.4 ENVIRONMENT AND EPIGENETICS IN NEUROLOGICAL HEALTH AND DISEASE

Numerous disorders of mental health and neurology are linked with interactions between multiple genetic and environmental factors, including nutrition. It is

now appreciated that epigenetic mechanisms are involved in many of these actions, and these are discussed in the following sections.

1.4.1 Epigenetics: Development and Metabolism

Many epigenetic processes play a critical role in neurological development, plasticity, learning, and memory [2–4, 42–44]. Epigenetics is a part of normal development, and a single genome gives rise to multiple cell-specific epigenomes in different tissues and organs. This explains the phenotypic diversity of adult differentiated cells that arise from identical genomes. Moreover, neuronal activity can alter the epigenetic state of neuronal genes, and, in turn, these epigenetic changes can influence the future responses of neurons and hence have important consequences for brain function and dysfunction [45].

Development is operated by reversible epigenetic memories, with global DNA methylation and demethylation occurring over time [46]. As a part of normal development, in germ cells and early embryos, there are striking genome-wide removal and subsequent reestablishment of epigenetic information. Of particular significance was the realization that epigenetic mechanisms are reversible [47]. Not only do reversible epigenetic memories play a key role in development, but they are a mechanism by which nutritional factors could be used to ameliorate the effects of adverse environmental experience.

Metabolic mechanisms are also involved in epigenetic regulation [48]. Endogenous metabolites and cofactors regulate the activity of chromatin-modifying enzymes, providing a direct link between epigenetics and the cell's metabolic state. Integration of understanding in genomic, epigenomics, and metabolic regulatory mechanisms may further elucidate the role of nutrition in neurological function and dysfunction and provide new approaches to modulation of epigenetic processes for prevention and therapy.

1.4.2 Energy Status, Signaling Molecules, and Cognitive Function

Optimal mental health is associated with positive advantages including a general state of well-being—the ability to learn, interact with others, and cope with change and uncertainty. Cultural, social, economic, and environmental factors such as nutrition all contribute to mental health, cognitive function, and quality of life.

Many nutritional effects on cognition are mediated by changes in expression of multiple genes and associated regulatory networks [2, 3, 6, 49]. This involves effects on cell membranes, enzymes, neurotransmitters, metabolism, neurogenesis, and synaptic plasticity. Multiple nutrition–gene interactions are involved in these responses. Especially important, for example, are links between energy status and BDNF. 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, and nutrition can add to these effects. Moreover, the adverse effects of strenuous exercise or high-energy intake are related to an increase in reactive oxygen species, decrease in BDNF expression, and compromised synaptic plasticity and cognition.

Many other signaling molecules are also implicated in nutritional regulation of brain function. IGF-1 mediates the actions of BDNF, and the histone deacetylase sirtuin silent information regulator 1 (SIRT1) is modified by energy metabolism. Glucocorticoids, thyroid hormones, vitamins A and D, polyunsaturated fatty acids, and other ligands of the nuclear receptor superfamily may also play a pivotal role. Their receptors act as transcription factors to affect multiple genes via epigenetic changes involving histone acetylation and chromatin remodeling.

The circulatory systemic environment acts as a modulator of neurogenesis and brain aging, with the aging systemic milieu negatively regulating cognitive function [50]. Recent studies in mice have shown that young blood reverses age-related impairments in synaptic plasticity and cognitive function [51]. Systemic factors in young blood induce vascular and neurogenic rejuvenation in the aging mouse brain. Moreover, growth differentiation factor 11 (GDF11) can alone improve the cerebral vasculature and enhance neurogenesis [52]. GDF11 is a member of the transforming growth factor β (TGF-β) family, and its nutritional regulation at all life stages needs to be

investigated. Overall, the studies discussed in this section suggest novel approaches for prevention and therapy of neurological disorders.

1.4.3 Neuroepigenetics and Neurological Disorders

The field of neuroepigenetics has had a considerable impact on understanding of brain function and neurological disorders [3, 4, 42, 53–56]. Environmental modulation of epigenetic mechanisms is implicated in the onset and course of many neurological conditions including autism, eating disorders, depression, Parkinson's disease, Huntington's disease, multiple sclerosis, cognitive decline, dementia, Alzheimer's disease, and schizophrenia. Epigenetic mechanisms can mediate immediate and long-term responses to adverse experience, such as malnutrition and physiological stress, to affect disease susceptibility and the course of neurodegenerative events.

Alzheimer's Disease Evidence suggests that complex epigenetic modifications are involved in Alzheimer's disease, confirming that environmental factors play a key role in this devastating disorder [3, 42, 57, 58]. Indeed, epigenetic mechanisms may provide a unique integrative framework for the pathologic diversity and complexity of Alzheimer's [59].

Epigenetic changes in the brains of Alzheimer's patients and in models of the disease involve DNA methylation, histone modifications, and noncoding microRNAs at multiple loci. Genome-wide results indicate decreases in DNA methylation markers in cortical neurons from Alzheimer's patients compared with elderly controls, whereas there are no such changes in the cerebellum, a region that is relatively spared in Alzheimer's.

The extent to which epigenetic changes in Alzheimer's disease and in normal aging are linked with nutrition is the subject of considerable current interest [4]. Specific nutrients including the dietary methyl donors folate, vitamins B6 and B12, choline, and methionine are essential for DNA methylation and optimal brain development and function. The probability is that nutrition throughout life markedly influences epigenetic marks in the brain, with concomitant effects on a wide range of neurological conditions including dementia.

The approval of epigenetic drugs for cancer treatment is advancing progress in the development of epigenetic drugs for treating neurodegenerative diseases including Alzheimer's [60, 61]. Methyl donors and histone deacetylase inhibitors are being investigated for possible therapeutic effects to rescue memory and cognitive decline found in such disorders. In the longer term, it may also be possible to use targeted nutritional intervention to prevent or ameliorate adverse epigenetic marks involved in the pathogenesis and pathology of the disease.

Schizophrenia Schizophrenia is a severe mental disorder with symptoms that include profound disruptions in thinking, hallucinations and delusions, and social and emotional dysfunction. The peak age of onset is in the 20s to early 30s, and it is associated with substantial costs. At the personal level, there are often unemployment, poverty, and homelessness. Life expectancy is reduced by 12–15 years because of the sedentary lifestyle, obesity, smoking, and suicide. Economically, the costs associated with schizophrenia can be greater than for all cancers combined.

Causes of schizophrenia are multifactorial and involve numerous interactions between genetic and environmental factors [2, 62, 63]. Epigenetic mechanisms are implicated in these interactions, although knowledge of the role of epigenetics in this field is limited and therefore should be interpreted with caution [64]. Nevertheless, genome-wide analysis on postmortem brain tissue suggests that differential DNA methylation is important in schizophrenia etiology [65].

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. The probability is that early-life environment plays a key role in schizophrenia and many other neurological disorders. Indeed, it is increasingly considered a neurodevelopmental disorder [56]. The neurodevelopmental hypothesis proposes schizophrenia to be related to genetic and environmental factors, leading to abnormal brain development during the prenatal or postnatal period. Moreover, first disease symptoms appear in early adulthood, during the synaptic pruning and myelination process.

1.5 EARLY NUTRITION, BRAIN DEVELOPMENT, AND LATER NEUROLOGICAL DISEASE

Nutrition plays a central role in linking the fields of developmental neurobiology and cognitive neuroscience. Optimal nutrition is essential for neurological

health: it has a profound impact on the development of brain structure and function, and malnutrition can result in both immediate and long-term neurological dysfunction [66–68]. Evidence suggests that both maternal nutrition and infant nutrition have a critical role in brain function and cognitive performance later in life [1, 2, 4, 69, 70].

Several disorders, ranging from cognitive impairment to schizophrenia, are related in part to neurodevelopmental insults such as malnutrition, hypoxia, viruses, or prenatal drug exposure. Advances in genomics and epigenomics are helping to elucidate the underlying mechanisms involved in the long-term effects of early nutrition on later disease. They highlight the importance of environment–gene interactions in this response. Figure 1.2 provides an overview of major interactions linking environment, genomics, and epigenomics in neurological health and disease.

1.5.1 Programming of Health and Disease

Environment–gene interactions are critical for brain function throughout life. Especially important is early-life experience: in adults, the incidence of numerous diseases is related in part to early nutrition, and these effects may even be transgenerational [4, 66, 71–74]. Both prenatal and postnatal nutrition can affect health and disease in later life, and epigenetic mechanisms are implicated in the programming of many diseases. These include metabolic disorders such as obesity and diabetes, cancers, and neurological disorders [2, 3].

Programming is the phenomenon whereby an insult, such as malnutrition, acting during a critical period of development 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 prenatally and postnatally, indicating that optimal nutrition is especially important during these early stages of the life cycle. The precise timing of critical periods is related to brain region and anatomical function. It is well recognized that prenatal life is a critical period for brain development. However, the relatively delayed rate of development of the human brain, compared with that of other mammals, can also make it especially susceptible to the influence of postnatal experience. The first 2 years of postnatal life are important because of the striking advances in brain structure and behavior that occur during this period. Moreover, from birth to teenage years, the volume of the human brain increases fourfold. During this period, there are also marked developments in motor, cognitive, and perceptual abilities.

1.5.2 Early Nutrition and Later Cognitive Function

Intrauterine growth restriction reflects a reduction in nutrient supply to the fetus, and infants born small for gestational age (SGA) and preterm have numerous nutritional deficits that can have immediate and long-term consequences for neurological function. These infants are at major risk of impaired neurodevelopment and multiple cognitive deficits in memory and learning [1, 2, 75]. Furthermore, size at birth across the weight range tends to be related to long-term cognitive function. Moreover, being born either SGA or large for gestational age (LGA) is associated with increased rates of obesity, metabolic disorder, and neurological disorders including attention-deficit/hyperactivity disorder, autism, anxiety, and depression [74]. Studies with humans and animal models indicate aberrant epigenetic mechanisms in the brains of SGA and LGA offspring, leading to disruptions in the cell cycle in development and gene expression in adulthood.

Maternal nutrition and infant nutrition have a critical role in cognitive performance later in life [1, 76, 77]. Prenatally, there is a positive association between maternal intake of nutrients including omega-3 fatty acids, iron, folate, and vitamin B12 and cognitive outcomes in children. Postnatally, breast milk is linked with enhanced neurodevelopment and may exert its beneficial effects in part via long-chain polyunsaturated fatty acids, IGFs, and iodine. In infants, a better diet quality score during the first 3 years of life has a positive effect on verbal and nonverbal cognitive ability at 10 years of age. Moreover, malnutrition during the first year of postnatal life carries significant risk for long-term cognitive function: infant malnutrition is associated with elevated incidence of impaired intelligence quotient and academic skills in adults, even when physical growth is rehabilitated [78].

Several key studies have focused on the impact of maternal diet on human milk composition and neurological development of human infants [76].

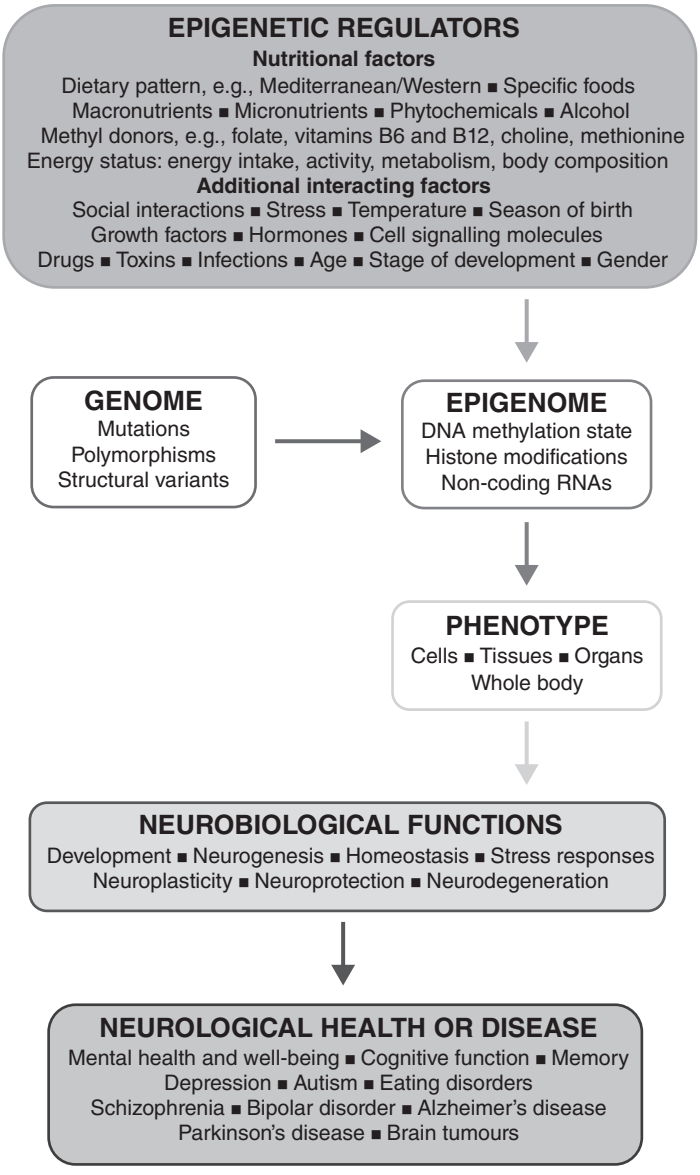

Fig. 1.2 Major interactions between environment, genomics, and epigenomics in neurological health and disease. *Source*: Based in part on Dauncey, M.J. Genomic and epigenomic insights into nutrition and brain disorders. *Nutrients* 2013, 5, 887–914. (*See insert for color representation of the figure*.)

The probability is that human milk fatty acid composition can alter infant neurological development. However, omega-3 fatty acid-rich oil supplements may not have the same implications for human milk quality and breastfed infants as a maternal diet in which part of the protein is provided by fish and other seafoods. In relation to gene variation and SNPs, in children who were breastfed as infants, there may be no effect of fatty acid desaturase (FADS) genotype on intelligence quotient. By contrast, in children who were not breastfed, gene variation in FADS and genes encoding fatty acid elongation are associated with cognitive development.

1.5.3 Nutritional Programming: Epigenetics and Neurology

Early-life experiences can trigger lifelong persisting epigenomic changes in the brain, with clear implications for the importance of nutrition in brain health and pathogenesis over the lifespan [3, 79]. Whether acquired neuroepigenetic changes can propagate through the germline and cause neurological change in subsequent generations is also of considerable interest [4].

Parental nutrition can critically affect both immediate and long-term development of the offspring, with effects being related both to energy status and specific nutrients. Newborns of obese parents have altered DNA methylation patterns of multiple imprinted genes [80]. Moreover, paternal obesity before conception is associated with IGF2 hypomethylation in newborns, suggesting that obesity adversely affects reprogramming of epigenetic marks during spermatogenesis [81]. However, deregulation of imprinting through a general effect on DNA methylation in differentially methylated regions is unlikely to be a common factor in developmental programming [82].

One-carbon units, including methyl donors, such as folate, vitamins B6 and B12, choline, and methionine, are essential for DNA methylation and epigenetic regulation of development [4, 83, 84]. In preterm and term newborn human infants, folate is associated with improved birth outcomes [85]. Maternal vitamin B12 status also has a role in fetal growth and development, and diets low in vitamin B12 and protein are associated with increased risk of neural tube defect and impaired neurodevelopment. Maternal dietary methyl supplements alter the phenotype of rat offspring by methylating the epigenome [86]. Key findings in humans also show that maternal dietary methyl donor intake around conception modulates DNA methylation at metastable epialleles in infants postnatally [87].

Maternal diet specifically affects global DNA methylation patterns in rat offspring brain [88]. Imbalance of folate and B12 results in brain DNA hypomethylation in the offspring at birth that is not normalized by postnatal nutrition. However, prenatal maternal omega-3 fatty acid supplementation normalized methylation at 3 months postnatally. More recent studies have now revealed that a maternal micronutrient imbalance alters gene expression of BDNF, nerve growth factor (NGF), and their signaling molecules, thereby adversely affecting the offspring brain at an adult age [89]. These findings highlight the importance of nutrient–nutrient interactions in modulating the expression of multiple genes linked with cognition and neurological function.

An added complexity is that nutrition could differentially affect gene expression in specific brain regions and cell types, and this may be especially important during early development [4]. Findings on DNA methylation profiling in the hippocampus and thalamus of postnatal malnourished mice indicate differences between brain regions and also emphasize the importance of postnatal malnutrition in increased risk of neuropsychiatric disorders [90]. Differences in epigenetic marks between tissues, brain regions, and cell types therefore need to be considered when the role of epigenetics in neurological disorders is investigated.

1.6 CONCLUSIONS

Nutrition–gene interactions are important throughout life, with prenatal and early postnatal development being especially critical periods of susceptibility. Effects may be beneficial or harmful, and consequences can be immediate or long term, with profound consequences for cognitive function and neurological disease. The actions of hormones, growth factors, and cell signaling molecules in mediating the actions of nutrition may be particularly significant. Moreover, knowledge of epigenomic dynamics highlights the importance of a lifelong approach to optimal nutrition, development, and health.

Significant interactions also occur between nutrition and many other environmental factors including stress, temperature, drugs, and infections. Together with other epigenetic regulators such as age, stage of development, and gender, these highly complex interactions exert profound effects on gene expression, phenotype, and neurological function. Individual gene variability adds a further level of control, with multiple polymorphisms and structural gene variants determining individual responses to nutrition and environment.

Future advances depend in part on increased links between nutrition studies and advances in genomics, epigenomics, and neuroscience. These could include very large-scale investigations of the whole genome and epigenomes of specific cell types, focused analysis of specific genes and

regulatory networks, assessment of functional connectivity between brain areas, and study of stem cell models of neurological disease. Technological progress combined with innovative approaches should result in significant advances in understanding nutrition–gene interactions and their role in optimal brain health and prevention or amelioration of many devastating neurological diseases.

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