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REVIEW

Nutrition, the brain and cognitive decline: insights from epigenetics

MJ Dauncey

Nutrition affects the brain throughout life, with profound implications for cognitive decline and dementia. These effects are mediated by changes in expression of multiple genes, and responses to nutrition are in turn affected by individual genetic variability. An important layer of regulation is provided by the epigenome: nutrition is one of the many epigenetic regulators that modify gene expression without changes in DNA sequence. Epigenetic mechanisms are central to brain development, structure and function, and include DNA methylation, histone modifications and non-protein-coding RNAs. They enable cell-specific and age-related gene expression. Although epigenetic events can be highly stable, they can also be reversible, highlighting a critical role for nutrition in prevention and treatment of disease. Moreover, they suggest key mechanisms by which nutrition is involved in the pathogenesis of age-related cognitive decline: many nutrients, foods and diets have both immediate and long-term effects on the epigenome, including energy status, that is, energy intake, physical activity, energy metabolism and related changes in body composition, and micronutrients involved in DNA methylation, for example, folate, vitamins B6 and B12, choline, methionine. Optimal brain function results from highly complex interactions between numerous genetic and environmental factors, including food intake, physical activity, age and stress. Future studies linking nutrition with advances in neuroscience, genomics and epigenomics should provide novel approaches to the prevention of cognitive decline, and treatment of dementia and Alzheimer's disease.

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INTRODUCTION

Multiple genetic and environmental factors, including nutrition, have a critical role in age-related cognitive decline, dementia and Alzheimer's disease. Advances in epigenetics are increasing understanding of the underlying mechanisms involved.[1] Appreciation of these highly complex mechanisms is suggesting new approaches to preventing and treating these devastating disorders. It also helps, in part, to explain inconsistencies between results from different studies on nutrition and brain function.

Cognition includes the mental processes involved in acquiring knowledge and the integration of these processes into numerous responses such as learning, decision-making, concentration and memory. The ageing process occurs throughout life, and ageing in later life can be associated with severe difficulties associated with cognitive decline and dementia. Cognitive decline involves an inability to reason, understand and interpret, and often also leads to dysfunctional behaviors. Dementia involves loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. The dysfunction is multifaceted and involves memory, behavior, personality, judgement, attention, language and other executive functions.

Previous comprehensive reviews have shown that nutrition affects brain structure and function throughout life.[2–4] Precise understanding of the links between nutrition and cognition is limited in part by the extreme complexity of the nutritional and neurological sciences, and their associated methodologies.[1,5] Nevertheless, it is well-established that numerous diets, foods and nutrients are involved and their effects can be beneficial or detrimental. Multiple brain processes that underpin cognitive function are affected by nutrition, including neurogenesis, synaptic plasticity and neuronal connectivity.[3,6] Responses can be immediate or long-term, with early-life nutrition having a significant impact on adult brain function. These effects are mediated by changes in expression of multiple genes and associated regulatory networks, and nutrition–gene interactions have important roles in optimal and sub-optimal cognitive function. Advances in genomics and epigenomics are increasing understanding of the mechanisms underlying nutrition–gene interactions and their role in health and disease. Epigenetics is emerging as perhaps the most important mechanism through which nutrition can directly influence the genome.[1,7,8]

This short review focuses on recent advances in understanding of the epigenetic mechanisms underpinning nutritional regulation of age-related cognitive decline and dementia. The focus is on recent state-of-the-art advances, and the reader is referred to review articles for earlier publications. First, a short overview is given on key aspects of nutrition that affect cognition: specific dietary components, energy status and early-life nutrition. Second, mechanisms underlying the epigenetic regulation of development, ageing and disease are discussed, especially in relation to neurological function. Third, the role of epigenetics in nutritional regulation of age-related cognitive decline is addressed, especially in relation to possible strategies for nutritional prevention and treatment of cognitive decline and dementia.

NUTRITION, THE BRAIN AND COGNITION

Specific dietary components

Studies using epidemiological, randomized control or intervention approaches link numerous dietary patterns, foods and nutrients with both beneficial and detrimental effects on brain function, cognition and dementia.[3,4,6,9–13] For example, a protective role has

Wolfson College, University of Cambridge, Cambridge, UK. Correspondence: Dr MJ Dauncey, Wolfson College, University of Cambridge, Cambridge CB3 9BB, UK.
E-Mail: mjd4@cam.ac.uk
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been reported for the Mediterranean diet, optimal energy status, fish, fruits, vegetables, flavonoids, polyunsaturated omega-3 fatty acids, zinc, copper and vitamins A, B, C, D and E. However, results can be inconsistent and this is, in part, because of methodological limitations associated with the multifactorial nature of the subject. The relation between nutrition and cognition is extremely complex and depends not only on age, sex and genetic variation but also on multiple dietary interactions, overall nutrient status, previous nutritional history and interactions with numerous additional environmental factors.[1,4]

Large groups and consortia are now focusing on many aspects of age-related brain function. For example, Cohort Studies of Memory in an International Consortium (COSMIC) aims to identify risk and protective factors and biomarkers of cognitive ageing and dementia in diverse ethnic and sociocultural groups.[14] The possibility is that this will help to identify further key aspects of nutrition involved in cognitive decline.

Energy status

Energy status has a central role in cognitive function and well-being throughout life.[4,15,16] The term energy status includes energy intake, physical activity, energy metabolism and related changes in body composition. This is a broader and less precise term than energy balance, and reflects the multifaceted influence of a critical component of nutritional status. Moreover, studies on physical activity tend not to control energy intake, while those on energy intake do not usually control physical activity. Numerous studies have demonstrated highly complex interactions between energy status and cognition. For example, both obesity and underweight are linked with impaired cognitive ability, cognitive decline and dementia.

Studies in adults clearly link physical activity, aerobic fitness and optimal energy intake with improved cognitive function.[4,6,17] Moreover, aerobic fitness in children benefits learning and memory, whereas inactivity is linked with poor cognitive health. Food restriction, without malnutrition, can be one of the most effective positive interventions for healthy ageing and lifespan. By contrast, overweight and obesity in middle and later life can increase risk of dementia. Paradoxically, however, weight loss or underweight immediately preceding and at the time of late-onset Alzheimer's disease may contribute to the onset and clinical progression of dementia.[5,18]

Early-life nutrition and programming of adult disease

Optimal nutrition is critical for brain function throughout life and especially important is early-life experience: in adults the incidence of numerous diseases is related in part to early nutrition.[2,4] Both prenatal and postnatal nutrition affect health and disease in later life, and these effects can even be passed between generations. Intrauterine growth restriction is a form of prenatal undernutrition that reflects a reduction in nutrient supply to the fetus. Infants born small-for-gestational age and preterm have numerous nutritional deficits that can have immediate and long-term consequences for cognitive health. They are at major risk of impaired neurodevelopment and multiple cognitive deficits in memory and learning. Furthermore, size at birth across the weight range is related to long-term cognitive function.

Considerable evidence also suggests that both maternal and infant nutrition have a critical role in brain function and cognitive performance later in life.[3,4,19–23] Prenatally, there is a positive association between maternal intake of micronutrients such as folate, vitamin B12, omega-3 polyunsaturated fatty acids and iron, and cognitive outcomes in children. Maternal supplementation with multiple nutrients may be especially beneficial, although considerably more research is needed in this area. Postnatally, breast milk is linked with enhanced neurodevelopment, and may exert its beneficial effects in part via long-chain polyunsaturated fatty acids and insulin-like growth factors (IGFs). Moreover, a better diet quality score during the first 3 years of life has a positive effect on verbal and non-verbal cognitive ability at 10 years of age. Especially important are recent results from a 40-year longitudinal study: moderate to severe malnutrition during infancy is associated with elevated incidence of impaired intelligence quotient and academic skills in adulthood, even when physical growth is rehabilitated.[24] This demonstrates that an episode of malnutrition during the first year of postnatal life carries significant risk for long-term cognitive function.

Underlying mechanisms: nutrition–gene interactions

Many of the diverse effects of nutrition on cognition are mediated by changes in expression of multiple genes and associated regulatory networks, with numerous gene variants adding a further level of complexity.[1,4,6,25] This involves effects on cell membranes, enzymes, neurotransmitters, metabolism, neurogenesis and synaptic plasticity. Energy status, for example, influences numerous hormones and growth factors that act as nutritional sensors to influence the brain via changes in gene expression. Molecules including glucocorticoids, thyroid hormones, insulin, IGFs and brain-derived neurotrophic factor (BDNF) are involved in multiple cell signaling systems and neural networks that mediate the actions of energy on the brain.

A critical layer of regulation is provided by the epigenome: nutrition is one of the many epigenetic regulators that modify gene expression without changes in DNA sequence.[1] Nutrition affects gene expression at levels of transcription, translation and post-translational modifications, and epigenetic mechanisms have a key role in some of these responses. An understanding of the role of epigenetics in regulating gene expression throughout life is therefore central to understanding of the role of nutrition in age-related cognitive decline and dementia. Recent advances in this area therefore form the basis of the following section.

EPIGENETICS IN DEVELOPMENT, AGEING AND DISEASE

Definitions of epigenetics

The term epigenetics means 'above genetics' and includes mechanisms that involve chemical marking of chromatin: 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. For example, DNA methylation reduces gene activity, and histone acetylation increases gene activity.

Precise definitions of epigenetics vary widely. It is concerned with changes in gene expression that are not caused by changes in DNA sequence. Depending on the area of study, investigators may be concerned with transient or stable effects, with the latter sometimes involving heritable effects between generations.[1,4,26] Most adult neuronal tissue is not mitotic and neuronal nuclei exit permanently from the cell cycle during prenatal development. Heritable maintenance in the brain may therefore be less of an issue than replication-independent methylation changes and chromatin remodeling.[27] Many factors, including nutrition, age, gender, physiological and psychological stress, chemicals and infections, exert powerful influences on the epigenetic regulation of gene expression.

Of particular interest in the nutritional context was the realization that epigenetic mechanisms are not irreversible or one-way but are reversible.[28] Indeed, reversible epigenetic memories have a key role in normal development. Epigenetics explains the phenotypic diversity of adult differentiated cells that arise from identical genomes.

Epigenetic mechanisms

Numerous epigenetic processes are involved in multiple highly complex, sophisticated mechanisms of gene regulation. These include changes in DNA methylation and hydroxymethylation, histone modifications, non-protein-coding RNAs (ncRNAs), RNA editing, chromatin remodeling and telomere control.[1,26,29] They enable cell-specific and age-related gene expression, and are central to normal brain development, structure and function. Thus, epigenetic signals have a critical role in synaptic plasticity, learning and memory.

It has long been recognized that DNA methylation has a pivotal role in gene regulation. Considerable advances are now also being made in understanding the complexity of the mechanisms involved in modulating other DNA methylation states. DNA methylation causes gene silencing via inhibition of transcription factor binding. It involves addition of methyl groups to cytosines, usually in CpG dinucleotides, to form 5-methyl cytosine (5 mc). This is carried out by three major DNA methyltransferases (DNMTs) that have distinct functional significance. Moreover, a series of major discoveries, including the finding that 5 mc can be oxidized to 5-hydroxymethyl cytosine (5 hmC) by ten–eleven translocation family enzymes, has significantly advanced understanding of active DNA demethylation.[30] It is now recognized that 5 hmC has a pivotal role in epigenetics, and in gene regulation, genome stability and development.

Epigenetics also involves post-translational modifications of histone proteins. These were long thought to be inert structural proteins around which DNA is wrapped and packaged as chromatin. However, histones are now appreciated as key players in epigenetics. Indeed, many epigenetic modifications take place in the context of chromatin. Histone acetylation, for example, increases gene expression by promoting the relaxed form of chromatin, hence enabling access of key transcription factors to relevant genes. Histone modifications are important markers of function and chromatin state and yet the DNA sequence elements that direct them to specific genomic locations are poorly understood. Recent studies have now identified hundreds of quantitative trait loci, genome-wide, that affect histone modifications in human cells.[31]

Less than 2% of the human genome codes for proteins, and most of the genome give rise to ncRNAs that nevertheless have a key role in development, health and disease.[1,32] They act as regulators of transcription, epigenetic processes and gene silencing, and individual variation at non-coding regulatory sequences adds a further level of complexity. Dramatic advances in RNA biology over recent years is of particular significance to an understanding of the brain, because neurons are highly transcriptionally active and demonstrate strong expression of ncRNAs. Many ncRNAs have a vital role in normal brain function and are involved in neural development, plasticity, memory and cognition.[29] Epigenetic processes are often involved, suggesting key interactions between ncRNAs and environmental factors such as nutrition.[1]

In addition to the molecular processes described above, metabolic mechanisms appear to have a key role in epigenetic regulation.[33] Endogenous cofactors and metabolites regulate the activity of chromatin-modifying enzymes, providing a direct link between the cell's metabolic state and epigenetics. Therefore, integration of understanding in genomic and metabolic regulatory mechanisms may further elucidate the role of nutrition in disease, and provide new approaches to modulation of epigenetic processes for prevention and therapy.

Developmental epigenetics

Development is operated by reversible epigenetic memories, with global DNA methylation and demethylation occurring over time. As a part of normal development, in germ cells and early embryos there is striking genome-wide removal and subsequent re-establishment of epigenetic information.[34,35] Errors can occur in this removal of epigenetic memory, making very early development an especially critical period that potentially impacts long-term health and may even extend to future generations. After this dramatic epigenetic reprogramming, it was originally thought that DNA methylation marks were permanent. However, although relatively stable, it is now appreciated that they can be modified by environmental factors, including nutrition, suggesting further mechanisms by which immediate and long-term health can be affected.

Especially important in very early development is the epigenetic regulation of imprinted genes.[28,36,37] A false but commonly held assumption is that the paternal and maternal genomes contribute equally to embryonic development. However, many genes demonstrate non-equivalence in activity of the parental genomes. Genomic imprinting is an epigenetic phenomenon whereby in some genes only one parental allele is expressed, while the other parental copy of the gene is silenced by DNA methylation.

Epigenetic mechanisms are essential for optimal development of multiple brain regions. Recent findings show that DNA methylation has a key role in establishing the gene expression potential of diverse hypothalamic cell types.[38] They provide the novel insight that in mice early postnatal life is a critical period for epigenetic development that distinguishes between neuronal and non-neuronal cells. Moreover, neurological plasticity mechanisms, regulated by both genetics and epigenetics, have a role in the brain from early development to late ageing.[39] For example, neocortical gene expression regulates mechanisms that impact critical periods for sensory and motor plasticity in ageing.

Neuroepigenetics and age-related disorders

Epigenetic mechanisms have an important role in many brain disorders including age-related cognitive decline, dementia and Alzheimer's disease. Over the past decade the field of neuroepigenetics has had considerable impact on understanding of brain development, ageing and function.[1,29,40,41] Many areas are still at the level of fascinating implications but considerable progress is also being made into the role of pharmacological and nutritional interventions for novel approaches to prevention and neurotherapy.

The human prefrontal cortex is essential for cognition and is one of the last brain regions to mature. The role of epigenetics in cortical development across the lifespan was examined in a genome-wide study of DNA methylation in ~14 500 genes at ~27 000 CpG loci focused on 50 promoter regions in post-mortem samples from 108 individuals aged from 14 weeks of gestation to 83 years.[42] DNA methylation showed unique temporal patterns across life. The fastest changes occur prenatally, slow down markedly after birth and continue to slow further with ageing. At the genome level, the transition from fetal to postnatal life is linked with demethylation prenatally to increased methylation postnatally. A limitation of this study was that it could not distinguish between methylation and 5-hydroxymethylation of cytosine, even though both have important roles in regulating brain gene expression. Nevertheless, it emphasizes the importance of prenatal and postnatal life as critical periods for nutritional modulation of brain function at the epigenetic level.

Degradation of epigenetic information is a consequence of healthy ageing and inevitably leads to functional decline.[26,43–45] There is imperfect maintenance of epigenetic marks over time, and changes in chromatin structure and DNA methylation throughout life may contribute to the ageing process and underlie many age-related diseases. Genome-wide studies in ageing cells and tissues have uncovered DNA methylation drift, that is, gradual increases or decreases over time that could potentially restrict the plasticity of stem cells. This leads to the possibility that prevention

or reduction in epigenetic drift could alleviate disorders and diseases associated with ageing. Findings from post-mortem human brain demonstrate involvement of DNA methylation and hydroxymethylation in Alzheimer's disease and emphasize the need to determine the timing of these epigenetic changes during the progression of Alzheimer's pathology.[46] MicroRNAs, a subgroup of ncRNAs, also have an important role in the control of brain development and ageing, and are associated with neurological disorders such as Alzheimer's. They are involved in post-transcriptional control of gene expression and also interact closely with other epigenetic mechanisms and create reciprocal regulatory circuits that appear to be disrupted in neuronal and glial cells affected by Alzheimer's disease.[47] For example, some microRNAs are regulated by promoter DNA methylation and/or chromatin modifications.

Oxidative stress plays a key role in age-associated diseases. The accumulation of intracellular damage due to reactive oxygen species may be involved in the functional impairment of aged tissues and contribute to the pathogenesis of Alzheimer's disease.[48] It is now recognized that age-related diseases are associated with changes in the genome and epigenome, and epigenetic mechanisms may have important pathophysiological roles in the presence of oxidative stress.

Of additional relevance is the knowledge that persistent memory and learning disabilities may occur postoperatively. This can be a particular problem in people with cognitive decline and dementia because although all age groups are affected, it can last for months in the elderly. Risk factors associated with post-operative cognitive dysfunction include exposure to general anesthesia, hypotension and hippocampal inflammation induced by the surgery. It has been postulated that these induce epigenetic dysfunction in the brain, since chromatin remodeling is necessary for memory-associated gene expression.[49] Awareness of this possibility highlights the particular need for optimal nutritional and clinical support in the elderly after surgery, to optimize cognitive function.

Gene variants

Common gene variants affect epigenetic mechanisms and thus increase individual differences in disease susceptibility.[31] Studies in newborns and pregnant women support the hypothesis that genetic variation in DNA methylating enzymes (DNMTs) influences DNA methylation.[50] Recent evidence from a large birth cohort further highlights the importance of epigenetics, combined with genetic variability, in birth outcomes.[51] Investigation of over 1000 mothers and newborns focused on polymorphisms in DNMTs and the imprinted genes PEG3, SNRPN and IGF2. Findings suggested an important role for epigenetics in birth outcome and health in early life. The DNMT3L allele in the baby was associated with higher birth weight and length, whereas the DNMT3B allele in the mother was associated with an increased risk of prematurity.

NUTRITION AND COGNITIVE DECLINE: THE ROLE OF EPIGENETICS

Nutrition–epigenetic interactions are implicated in age-related cognitive decline and dementia.[1,52] Epigenetic modifications affect gene expression in multiple physiological and pathological brain processes, and are an integral part of numerous brain functions. They are plastic and reversible, suggesting a mechanism for nutritional prevention or treatment of cognitive decline and dementia. Nutrition could be used throughout life to enhance neurological function and alleviate the adverse effects of early-life experience on later brain function.

Specific dietary components and anti-ageing epigenetic diets

Advances in epigenetics are providing the basis for nutritional interventions in adults that may prevent or alleviate cognitive decline and dementia.[53] Anti-ageing epigenetic diets include a restricted energy intake with adequate nutrient supply, supplementation with nutrients involved in one-carbon metabolism and the concomitant provision of methyl groups, and supplementation with bioactive food components. Current studies using these diets have limitations and the use of appropriate models is currently being assessed by the ongoing European project NU-AGE (http://www.nu-age.eu/home). This multidisciplinary consortium of 30 partners from 17 European Union countries focuses on increasing knowledge on how the whole diet can have an impact on and counteract age-related disease and functional decline.

Throughout life the dietary supply of methyl donors such as folate, vitamins B6 and B12, choline and methionine is essential for optimal growth and physiological function.[23,54] One-carbon pathways donate and regenerate one-carbon units, including the methyl group that is essential for DNA methylation. Understanding of factors regulating maternal–fetal one-carbon metabolism and its role in early-life programming of adult disease may help in designing optimal strategies for effective interventions. For example, maternal vitamin B12 status has a key role in fetal growth and development, and diets low in vitamin B12 and protein are associated with increased risk of neural tube defect, excess adiposity and impaired neurodevelopment.

Investigations of genetic and non-genetic influences during pregnancy on infant global and site-specific DNA methylation have highlighted important roles for folate gene variants and vitamin B12 status of infants and mothers.[55] Assessment of seven polymorphisms in six genes involved in folate absorption and metabolism, together with blood levels of folate and vitamin B12, demonstrated that environmental and genetic factors involved in one-carbon metabolism influence DNA methylation in infants. Especially important are findings that maternal folate depletion and high-fat feeding from weaning affects DNA methylation and DNA repair in brain of adult mouse offspring.[56] This suggests that low folate nutrition in early life may leave an epigenetic mark that predisposes the offspring to further dietary insults, thus adding to the adverse effects of early-life malnutrition on adult health.

Diet affects not only DNA methylation but also histone modifications and ncRNAs. For example, the polyphenol kaempferol acts as an inhibitor of oxidative stress and has been identified as a novel inhibitor of histone deacetylases.[57] Several studies suggest a role for vitamin D in brain development and function, and there is a significant association between low levels of vitamin D and Alzheimer's disease.[58] Alterations in the epigenetic regulators, microRNAs, have a key role in Alzheimer's pathogenesis. Therefore, of particular interest is the finding that vitamin D supplements may have a beneficial effect on Alzheimer's, in part via microRNAs.

Energy status, epigenetics and cognition

There is a close relation between energy metabolism and epigenetic events, and bioenergetics provides the interface between environment and the epigenome.[1,6] Optimal energy status enhances mental health and cognition in part by epigenetic remodeling of chromatin containing the BDNF gene, resulting in BDNF-induced brain plasticity in the hippocampus, a key brain region for cognition. Many other signaling molecules are also involved. For example, 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 super-family may also have a pivotal role in mediating the effects of nutrition on brain function.

Their receptors act as transcription factors to affect multiple genes via epigenetic changes involving histone acetylation and chromatin remodeling.

Restriction of energy intake, without malnutrition, is a highly effective intervention for age-related functional decline. Dietary energy restriction may have a neuroprotective effect on the ageing brain via its effects on decreasing oxidative stress and reducing apoptosis. Multiple age-related changes in gene expression are partially or completely prevented by a reduction in energy intake, and these effects are mediated in part by epigenetic mechanisms. Ageing in the hippocampus, a key brain area for cognitive function, is associated with aberrant epigenetic marks including effects on DNA methylation and hydroxymethylation, DNMT3A and histone deacetylase.[46,52] SIRT1 may also be involved in the beneficial effects of dietary restriction in extending lifespan and enhancing healthy ageing. Findings from SIRT1 overexpression and knockdown in a human cell line suggest that some of these effects are mediated by DNA methylation.[59] This indicates that gene expression changes via epigenetic modifications are one of the mechanisms underlying the response to dietary restriction. Moreover, the dietary polyphenol resveratrol acts as a SIRT1 mimic and also increases longevity.

Obesity is a major risk factor for cognitive decline and recent studies have identified a central role for epigenetics in this response.[60,61] This suggests possible approaches to the development of novel therapeutic interventions and predictive biomarkers. Epidemiological evidence that epigenetic mechanisms underlie a propensity for overweight is supported by recent molecular studies. In primary human adipocytes, genome-wide specific histone H3 methylation was found to be directly associated with overweight and type 2 diabetes.[62]

Early-life nutrition, epigenetics and cognition

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.[1,41] Moreover, whether acquired neuroepigenetic changes can propagate through the germline and cause behavioral change in subsequent generations is the subject of considerable debate and significance.

Many imprinted genes, such as the IGF2-H19 complex, have key roles in placental, embryonic and fetal growth and development. Newborns of obese parents have altered DNA methylation patterns at multiple imprinted genes.[63] Moreover, paternal obesity is associated with IGF2 hypomethylation in newborns.[64] This study showed that preconceptional paternal obesity affects reprogramming of imprint marks during spermatogenesis, with potential adverse consequences for future health of the offspring. Evidence in mice does suggest, however, that deregulation of imprinting through a general effect on DNA methylation in differentially methylated regions is unlikely to be a common factor in developmental programming.[65] Maternal obesity also affects epigenetic mechanisms in offspring that may have adverse long-term effects on cognitive function. Obesity and diabetes induce latent metabolic defects and widespread epigenetic changes in mouse offspring.[66] Expression of multiple genes in specific brain regions is affected, and may alter the developmental program of key fetal brain cell networks involved in neurological disorders in later life.[67]

An optimal supply of methyl donors is essential for epigenetic regulation of immediate and long-term brain function. Assessment of folate and thiamine status in preterm and term newborn human infants suggests that folate in particular is associated with improved birth outcomes.[68] Two especially important studies have emphasized the critical role of maternal diet on brain global DNA methylation patterns in rat offspring.[69,70] Detailed investigations focused on folate and vitamin B12. Maternal micronutrient imbalance resulted in brain DNA hypomethylation in the offspring at birth that was not normalized by postnatal nutrition. However, prenatal maternal omega-3 fatty acid supplementation normalized methylation at 3 months postnatally, emphasizing its key role in long-term brain function. These findings also demonstrate the importance of nutrient–nutrient interactions in modulating the expression of multiple genes linked with long-term neuroprotection and cognition.

CONCLUSIONS

This review highlights the critical role of multiple complex interactions between nutrition and epigenetics in age-related cognitive decline and dementia. It emphasizes the importance of a life-long approach to nutritional prevention of these devastating disorders. In view of marked differences in multiple gene variants, an individualized approach should be used in infants, children, adolescents and all stages of adult life. Ideally, the focus needs to be on optimal energy status in relation to food intake, activity, body composition and a balanced Mediterranean diet. However, if it is impossible to improve food intake and activity, as may be the case particularly in elderly people, then the focus should be on key nutrients. Considerably more research is needed in this area, especially in relation to individual variability in coding and non-coding regions of the genome. Current evidence suggests, however, that key nutrients for optimal cognition include omega-3 fatty acids such as docosahexaenoic acid and dietary methyl donors such as B vitamins.

Numerous factors interact with nutrition to affect cognitive function.[1,4] Stress can severely impair cognition, with effects being immediate and long-term. The possibility is that early nutrition together with stress hormones and sensory stimuli from the mother act synergistically to program the adult brain, in part via epigenetic mechanisms.[71] Understanding how multiple inputs from nutrition, other epigenetic regulators and genetic variability affect the developing and adult brain should result in development of effective preventative and therapeutic approaches to age-related cognitive decline and dementia.

In the future, stronger links between nutrition studies and advances in neuroscience, genomics and epigenomics should provide new approaches to prevention of cognitive decline and treatment of dementia. Significant advances are currently being made in neuroscience using approaches that range from stem cell models of Alzheimer's disease and related neurological disorders,[72] to brain-wide magnetic resonance imaging of age-related changes in functional connectivity between brain areas.[73] Similar approaches could be used to investigate the role of nutrition in neuroscience and cognition, in studies ranging from nutrient–nutrient interactions at the single-cell level, to the effects of energy status and the Mediterranean diet at the whole-brain level. Further links could also be made between nutrition studies and Big Data projects including the 1000 Genomes Project (http://www.1000genomes.org/) and Human Epigenome Project (http://www.epigenome.org/). These projects should provide unprecedented insight into the individual variability of coding and non-coding genes, and the complex relationship between genetics and epigenetics in multiple tissues and cell types. In the long-term, they should also suggest novel approaches for personalized nutritional prevention of cognitive decline and dementia.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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REFERENCES

1 Dauncey MJ. Genomic and epigenomic insights into nutrition and brain disorders. *Nutrients* 2013; **5**: 887–914.
2 Dauncey MJ, Bicknell RJ. Nutrition and neurodevelopment: mechanisms of developmental dysfunction and disease in later life. *Nutrition Res Rev* 1999; **12**: 231–253.
3 Dauncey MJ. New insights into nutrition and cognitive neuroscience. *Proc Nutr Soc* 2009; **68**: 408–415.
4 Dauncey MJ. Recent advances in nutrition, genes and brain health. *Proc Nutr Soc* 2012; **71**: 581–591.
5 Fielding RA, Gunstad J, Gustafson DR, Heymsfield SB, Kral JG, Launer LJ *et al.* The paradox of overnutrition in aging and cognition. *Ann NY Acad Sci* 2013; **1287**: 31–43.
6 Gomez-Pinilla F, Tyagi E. Diet and cognition: interplay between cell metabolism and neuronal plasticity. *Curr Opin Clin Nutr Metab Care* 2013; **16**: 726–733.
7 Choi SW, Claycombe KJ, Martinez JA, Friso S, Schalinske KL. Nutritional epigenomics: a portal to disease prevention. *Adv Nutr* 2013; **4**: 530–532.
8 Haggarty P. Epigenetic consequences of a changing human diet. *Proc Nutr Soc* 2013; **72**: 363–371.
9 Gillette-Guyonnet S, Secher M, Vellas B. Nutrition and neurodegeneration: epidemiological evidence and challenges for future research. *Br J Clin Pharmacol* 2013; **75**: 738–755.
10 Alzheimer'sDiseaseInternational. Nutrition and dementia. A review of available research: http://www.alz.co.uk/nutrition-report, 2014.
11 Hennebelle M, Plourde M, Chouinard-Watkins R, Castellano CA, Barberger-Gateau P, Cunnane SC. Ageing and apoE change DHA homeostasis: relevance to age-related cognitive decline. *Proc Nutr Soc* 2014; **73**: 80–86.
12 Mangialasche F, Solomon A, Kareholt I, Hooshmand B, Cecchetti R, Fratiglioni L *et al.* Serum levels of vitamin E forms and risk of cognitive impairment in a Finnish cohort of older adults. *Exp Gerontol* 2013; **48**: 1428–1435.
13 Swaminathan S, Edward BS, Kurpad AV. Micronutrient deficiency and cognitive and physical performance in Indian children. *Eur J Clin Nutr* 2013; **67**: 467–474.
14 Sachdev PS, Lipnicki DM, Kochan NA, Crawford JD, Rockwood K, Xiao S *et al.* COSMIC (Cohort Studies of Memory in an International Consortium): an international consortium to identify risk and protective factors and biomarkers of cognitive ageing and dementia in diverse ethnic and sociocultural groups. *BMC Neurol* 2013; **13**: 165.
15 Besser LM, Gill DP, Monsell SE, Brenowitz W, Meranus DH, Kukull W *et al.* Body mass index, weight change, and clinical progression in mild cognitive impairment and Alzheimer disease. *Alzheimer Dis Assoc Disord* 2014; **28**: 36–43.
16 Rizza W, Veronese N, Fontana L. What are the roles of calorie restriction and diet quality in promoting healthy longevity? *Ageing Res Rev* 2014; **13C**: 38–45.
17 Raine LB, Lee HK, Saliba BJ, Chaddock-Heyman L, Hillman CH, Kramer AF. The influence of childhood aerobic fitness on learning and memory. *PloS One* 2013; **8**: e72666.
18 Gustafson DR. Adiposity and cognitive decline: underlying mechanisms. *J Alzheimers Dis* 2012; **30**: S97–112.
19 Agostoni C, Manzoni P. Nutrition and neurocognitive development. *Early Hum Dev* 2013; **89**: S1–S3.
20 Anjos T, Altmae S, Emmett P, Tiemeier H, Closa-Monasterolo R, Luque V *et al.* Nutrition and neurodevelopment in children: focus on NUTRIMENTHE project. *Eur J Nutr* 2013; **52**: 1825–1842.
21 Nyaradi A, Li J, Hickling S, Foster J, Oddy WH. The role of nutrition in children's neurocognitive development, from pregnancy through childhood. *Front Hum Neurosci* 2013; **7**: 97.
22 Nyaradi A, Li J, Hickling S, Whitehouse AJ, Foster JK, Oddy WH. Diet in the early years of life influences cognitive outcomes at 10 years: a prospective cohort study. *Acta Paediatr* e-pub ahead of print 23 July 2013; doi:10.1111/apa.12363.
23 Rush EC, Katre P, Yajnik CS. Vitamin B12: one carbon metabolism, fetal growth and programming for chronic disease. *Eur J Clin Nutr* 2014; **68**: 2–7.
24 Waber DP, Bryce CP, Girard JM, Zichlin M, Fitzmaurice GM, Galler JR. Impaired IQ and academic skills in adults who experienced moderate to severe infantile malnutrition: a 40-year study. *Nutr Neurosci* 2014; **17**: 58–64.
25 European Alzheimer's Disease I, Genetic, Environmental Risk in Alzheimer's D, Alzheimer's Disease Genetic C, Cohorts for H, Aging Research in Genomic E. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet* 2013; **45**: 1452–1458.
26 Murrell A, Hurd PJ, Wood IC. Epigenetic mechanisms in development and disease. *Biochem Soc Trans* 2013; **41**: 697–699.
27 Meaney MJ, Ferguson-Smith AC. Epigenetic regulation of the neural transcriptome: the meaning of the marks. *Nature NeuroscI* 2010; **13**: 1313–1318.
28 Ishino F, Shinkai Y, Whitelaw E. Mammalian epigenetics in biology and medicine. *Philos Trans R Soc Lond B Biol Sci* 2013; **368**: 20120386.
29 Qureshi IA, Mehler MF. Understanding neurological disease mechanisms in the era of epigenetics. *JAMA Neurol* 2013; **70**: 703–710.
30 Kohli RM, Zhang Y. TET enzymes, TDG and the dynamics of DNA demethylation. *Nature* 2013; **502**: 472–479.
31 McVicker G, van de Geijn B, Degner JF, Cain CE, Banovich NE, Raj A *et al.* Identification of genetic variants that affect histone modifications in human cells. *Science* 2013; **342**: 747–749.
32 Kornienko AE, Guenzl PM, Barlow DP, Pauler FM. Gene regulation by the act of long non-coding RNA transcription. *BMC Biol* 2013; **11**: 59.
33 Meier JL. Metabolic mechanisms of epigenetic regulation. *ACS Chem Biol* 2013; **8**: 2607–2621.
34 Reik W, Dean W, Walter J. Epigenetic reprogramming in mammalian development. *Science* 2001; **293**: 1089–1093.
35 Seisenberger S, Andrews S, Krueger F, Arand J, Walter J, Santos F *et al.* The dynamics of genome-wide DNA methylation reprogramming in mouse primordial germ cells. *Mol Cell* 2012; **48**: 849–862.
36 Kelsey G, Feil R. New insights into establishment and maintenance of DNA methylation imprints in mammals. *Philos Trans R Soc Lond B Biol Sci* 2013; **368**: 20110336.
37 Seisenberger S, Peat JR, Hore TA, Santos F, Dean W, Reik W. Reprogramming DNA methylation in the mammalian life cycle: building and breaking epigenetic barriers. *Philos Trans R Soc Lond B Biol Sci* 2013; **368**: 20110330.
38 Li G, Zhang W, Baker MS, Laritsky E, Mattan-Hung N, Yu D *et al.* Major epigenetic development distinguishing neuronal and non-neuronal cells occurs postnatally in the murine hypothalamus. *Hum Mol Genet* 2013; **23**: 1579–1590.
39 Huffman K. The developing, aging neocortex: how genetics and epigenetics influence early developmental patterning and age-related change. *Front Genet* 2012; **3**: 212.
40 Akbarian S, Beeri MS, Haroutunian V. Epigenetic determinants of healthy and diseased brain aging and cognition. *JAMA Neurol* 2013; **70**: 711–718.
41 Sweatt JD. The emerging field of neuroepigenetics. *Neuron* 2013; **80**: 624–632.
42 Numata S, Ye T, Hyde TM, Guitart-Navarro X, Tao R, Wininger M *et al.* DNA methylation signatures in development and aging of the human prefrontal cortex. *Am J Hum Genet* 2012; **90**: 260–272.
43 Horvath S. DNA methylation age of human tissues and cell types. *Genome BIol* 2013; **14**: R115.
44 Issa JP.Aging and epigenetic drift: a vicious cycle. *J Clin Investig* 2014; **124**: 24–29.
45 Weidner CI, Lin Q, Koch CM, Eisele L, Beier F, Ziegler P *et al.* Aging of blood can be tracked by DNA methylation changes at just three CpG sites. *Genome Biol* 2014; **15**: R24.
46 Chouliaras L, Mastroeni D, Delvaux E, Grover A, Kenis G, Hof PR*et al.* Consistent decrease in global DNA methylation and hydroxymethylation in the hippocampus of Alzheimer's disease patients. *Neurobiol Aging* 2013; **34**: 2091–2099.
47 Van den Hove DL, Kompotis K, Lardenoije R, Kenis G, Mill J, Steinbusch HW *et al.* Epigenetically regulated microRNAs in Alzheimer's disease. *Neurobiol Aging* 2014; **35**: 731–745.
48 Cencioni C, Spallotta F, Martelli F, Valente S, Mai A, Zeiher AM *et al.* Oxidative stress and epigenetic regulation in ageing and age-related diseases. *Int J Mol Sci* 2013; **14**: 17643–17663.
49 Wang Y, Chen Z, Zhao Y, Shi R, Wang Y, Xu J *et al.* Epigenetics as a new therapeutic target for postoperative cognitive dysfunction. *Med Hypotheses* 2013; **80**: 249–251.
50 Potter C, McKay J, Groom A, Ford D, Coneyworth L, Mathers JC *et al.* Influence of DNMT genotype on global and site specific DNA methylation patterns in neonates and pregnant women. *PLoS One* 2013; **8**: e76506.
51 Haggarty P, Hoad G, Horgan GW, Campbell DM. DNA methyltransferase candidate polymorphisms, imprinting methylation, and birth outcome. *PLoS One* 2013; **8**: e68896.
52 Chouliaras L, van den Hove DL, Kenis G, Keitel S, Hof PR, van Os J *et al.* Age-related increase in levels of 5-hydroxymethylcytosine in mouse hippocampus is prevented by caloric restriction. *Curr Alzheimer Res* 2012; **9**: 536–544.

53 Bacalini MG, Friso S, Olivieri F, Pirazzini C, Giuliani C, Capri M*et al.* Present and future of anti-ageing epigenetic diets. *Mech Ageing Dev* 2014; **136-137**: 101–115.
54 Kalani A, Kamat PK, Givvimani S, Brown K, Metreveli N, Tyagi SC*et al.* Nutri-epigenetics ameliorates blood-brain barrier damage and neurodegeneration in hyperhomocysteinemia: role of folic acid. *J Mol Neurosci.* 2013; **52**: 202–215.
55 McKay JA, Groom A, Potter C, Coneyworth LJ, Ford D, Mathers JC *et al.* Genetic and non-genetic influences during pregnancy on infant global and site specific DNA methylation: role for folate gene variants and vitamin B12. *PLoS One* 2012; **7**: e33290.
56 Langie SA, Achterfeldt S, Gorniak JP, Halley-Hogg KJ, Oxley D, van Schooten FJ *et al.* Maternal folate depletion and high-fat feeding from weaning affects DNA methylation and DNA repair in brain of adult offspring. *FASEB J* 2013; **27**: 3323–3334.
57 Berger A, Venturelli S, Kallnischkies M, Bocker A, Busch C, Weiland T *et al.* Kaempferol, a new nutrition-derived pan-inhibitor of human histone deacetylases. *J Nutr Biochem* 2013; **24**: 977–985.
58 Lu'o'ng KV, Nguyen LT. The role of vitamin D in Alzheimer's disease: possible genetic and cell signaling mechanisms. *Am J Alzheimers Dis Other Demen* 2013; **28**: 126–136.
59 Ions LJ, Wakeling LA, Bosomworth HJ, Hardyman JE, Escolme SM, Swan DC *et al.* Effects of Sirt1 on DNA methylation and expression of genes affected by dietary restriction. *Age (Dordr)* 2013; **35**: 1835–1849.
60 Burdge GC, Lillycrop KA. Environment-physiology, diet quality and energy balance: The influence of early life nutrition on future energy balance. *Physiol Behav* 2014; **134**: 119–122.
61 Martinez JA, Milagro FI, Claycombe KJ, Schalinske KL. Epigenetics in adipose tissue, obesity, weight loss, and diabetes. *Adv Nutr* 2014; **5**: 71–81.
62 Jufvas A, Sjodin S, Lundqvist K, Amin R, Vener AV, Stralfors P. Global differences in specific histone H3 methylation are associated with overweight and type 2 diabetes. *Clin Epigenetics* 2013; **5**: 15.
63 Soubry A, Murphy SK, Wang F, Huang Z, Vidal AC, Fuemmeler BF *et al.* Newborns of obese parents have altered DNA methylation patterns at imprinted genes. *Int J Obes (Lond)* e-pub ahead of print 25 October 2013; doi:10.1038/ijo.2013.193.
64 Soubry A, Schildkraut JM, Murtha A, Wang F, Huang Z, Bernal A *et al.* Paternal obesity is associated with IGF2 hypomethylation in newborns: results from a Newborn Epigenetics Study (NEST) cohort. *BMC Med* 2013; **11**: 29.
65 Ivanova E, Chen JH, Segonds-Pichon A, Ozanne SE, Kelsey G. DNA methylation at differentially methylated regions of imprinted genes is resistant to developmental programming by maternal nutrition. *Epigenetics* 2012; **7**: 1200–1210.
66 Li CC, Young PE, Maloney CA, Eaton SA, Cowley MJ, Buckland ME *et al.* Maternal obesity and diabetes induces latent metabolic defects and widespread epigenetic changes in isogenic mice. *Epigenetics* 2013; **8**: 602–611.
67 Stachowiak EK, Oommen S, Vasu VT, Srinivasan M, Stachowiak M, Gohil K *et al.* Maternal obesity affects gene expression and cellular development in fetal brains. *Nutritional Neurosci* 2013; **16**: 96–103.
68 Weber D, Stuetz W, Bernhard W, Franz A, Raith M, Grune T *et al.* 5-Methyltetrahydrofolate and thiamine diphosphate in cord-blood erythrocytes of preterm versus term newborns. *Eur J Clin Nutr* 2013; **67**: 1029–1035.
69 Sable P, Randhir K, Kale A, Chavan-Gautam P, Joshi S. Maternal micronutrients and brain global methylation patterns in the offspring. *Nutr Neurosci*; e-pub ahead of print 27 November 2013; doi:10.1179/1476830513Y.0000000097.
70 Sable PS, Kale AA, Joshi SR. Prenatal omega 3 fatty acid supplementation to a micronutrient imbalanced diet protects brain neurotrophins in both the cortex and hippocampus in the adult rat offspring. *Metabolism* 2013; **62**: 1607–1622.
71 Lucassen PJ, Naninck EF, van Goudoever JB, Fitzsimons C, Joels M, Korosi A. Perinatal programming of adult hippocampal structure and function; emerging roles of stress, nutrition and epigenetics. *Trends Neurosci* 2013; **36**: 621–631.
72 Livesey FJ. Stem cell models of Alzheimer's disease and related neurological disorders. *Alzheimer's Res Ther* 2012; **4**: 44.
73 Geerligs L, Renken RJ, Saliasi E, Maurits NM, Lorist MM. A brain-wide study of age-related changes in functional connectivity. *Cerebral Cortex*; e-pub ahead of print 13 February 2014; doi:10.1093/cercor/bhu012.