Special Report

Symposium on nutrition and cognition: towards research and application for different life stages

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A Symposium on Nutrition and Cognition: Towards Research and Application for Different Life Stages was held on October 2010 in Malaysia. The influence of diet and nutrition on the cognitive development of the child and on cognitive decline in later life was reviewed. Central to the study of such topics is the assessment of cognitive functioning. Cognitive functioning falls into six main areas: executive functioning, memory, attention, perception, psychomotor and language skills, although each domain can be further subdivided. As it is in the nature of human functioning that the performance on any cognitive test can reflect aspects of many of these domains, ideally a battery of tests should be used to establish the basis of any difference in performance. In intervention studies, frequently there has been a failure to demonstrate a beneficial influence of changes in diet. A possible reason is that studies have failed to acknowledge the time scale and critical ages over which diet has an impact. Diet may have a slow and progressive influence making it difficult for short-term studies to show an improvement. In addition, as many factors influence human behaviour, dietary interventions should only be one part of a coordinated approach; the effect of diet will depend on the social and psychological context in which an individual lives. Placing diet into a broader social and psychological context greatly increases the chance of generating significant findings. This report highlights and reviews presentations and discussions at the symposium.

Key Words: aging, brain development, cognition, cognitive decline, nutrition

INTRODUCTION

Southeast Asia still faces problems of inadequate nutrition in sections of the population; and to date most attention has been directed to preventing deficiency diseases, with an emphasis on the provision of adequate energy and protein, as well as specific nutrients such as iodine, iron and vitamin A. Both a deficiency of iodine and iron, when the brain is initially developing, results in irreversible damage. Vitamin A deficiency is the leading cause of preventable blindness in children; and in pregnant women, increases the risk of maternal mortality. However, in those sections of the population where clinical deficiency is no longer a problem, there arises an interest in ensuring that nutrition is sufficient to allow optimal cognitive development and to slow cognitive decline in later years. Therefore a symposium took place, entitled Nutrition and Cognition: Towards Research and Application for Different Life Stages, on October 19-21, 2010, in Kuala Lumpur Malaysia, to: 1) share the state-of-the-art knowledge on the relationship between nutrition and cognition; 2) highlight current methodologies in assessing cognitive functions, and explore their applicability for different population groups and life stages; 3) discuss issues relating to scientific substantiation of cognition related claims; and 4) consider consumer understanding of nutritional influences on cognition. The meeting was organized by the International Life Sciences Institute Southeast Asia Region, the Nutrition Society of Malaysia in collaboration with the Australian based Commonwealth Scientific and Industrial Research Organization.

The present report summarizes a wide-ranging and lively meeting during which there were a number of broad themes: 1) role of nutrition in cognitive development; 2) role of nutrition in cognitive performance and degeneration; 3) assessment of cognitive functions; and 4) evidence-based claims and consumer understanding on cognition. The choice of cognitive measures is crucial and must be relevant for the target population. There is no "one size fits all" cognitive battery that can be used in nutrition intervention studies, rather assessment tools need to be tailored to the target groups and research needs.

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Manuscript received 15 July 2011. Accepted 15 August 2011.

The impact of nutrition on cognition is likely to begin very early; nutrition in the pre-natal stage can be influential throughout the lifespan. Thus early nutrition was considered, but also nutrition in later life, as in South-East Asia the population is ageing rapidly with an expectation that the incidence of dementia will increase. How targeted nutrition can assist in both development and aging is being actively explored. There is potentially a characteristic Asian contribution to this area, given the history of using spices and herbs as traditional medicines, there is a potential to provide novel foods.

Asian cultures tend to take pride in their child being 'smart' but also favour a long and healthy life. Such factors generate a strong interest in the influence of nutrition on cognitive functioning at all life stages. It follows that consumer understanding of any nutritionally based claim, the form of the wording on the packet, is important. Not only does a claim need to be scientifically defensible but the words used need to communicate the intended meaning to the general public that is not likely to understand scientific jargon, while the small differences in meaning that are important to specialists are reasonably retained. In turn regulators require appropriate and substantial evidence for claims in the area of nutrition and cognition that are specific, quantifiable and relate to specific target groups.

The organization of this report reflects the topics considered during the meeting.

NUTRITION AND COGNITIVE DEVELOPMENT DURING GROWTH AND DEVELOPMENT

Protein-energy malnutrition adversely affects early development by changing structural proteins and the production of neurotransmitters.[1] Nutritional deficiency is common among women, infants and young children throughout the developing world. Whereas cost-effective interventions to alleviate these problems have been identified, global efforts continue to be necessary to harmonize these efforts by working with affected populations to improve the environment and hence human capacity.[2] The influence of several micronutrients on cognition has been explicitly identified as having a role in achieving the Millennium Development Goals (MDG). Micronutrient supplementation has a significant role in facilitating human development in the context of reducing the effects of poverty (MDG1) and enhancing primary education (MDG2), as well as promoting gender equity (MDG3). Moreover, an adequate micronutrient status helps to reduce common childhood infections, maternal morbidity and the outcome of pregnancy, leading to a reduction of child mortality (MDG4) and improved maternal health (MDG5).[3]

Prevalence of malnutrition worldwide

Globally, 13 million children are born annually with intrauterine growth restriction; 112 million are underweight, 55 million children are wasted, 19 million suffer from chronic and acute malnutrition. One hundred and seventy eight million children under five were stunted, mostly in south Asia and sub-Saharan Africa.[4] Maternal short stature (height <145 cm) was most prevalent in south Asia, and 10-19% of women aged 15–49 years had low body-mass index. Stunting, severe wasting, and intrauterine growth restriction together were responsible for about two million deaths and 21% of disability-adjusted life-years (DALYs) for children under five. In Asia, 31.3% and 22% of children under five were stunted (short stature) and underweight, respectively, and 3.7% were severely wasted (thin). South-central Asia had the highest prevalence of all of these undernourished conditions (stunting: 40.7%, 73.8 million; severe wasting: 5.7%, 10.3 million; underweight: 33.1%, 60.1 million), followed by Southeast Asia where 12.4% of term babies were born with a low birth weight (<2500 g), that reflected poor maternal nutrition and retardation of intrauterine growth. South-central Asia also has a high prevalence; 19.9% or approximately 8 million of live births are of a low weight. Inadequate breastfeeding was responsible for 1.4 million child deaths and 44 million or 10% of DALYs amongst those under five.[5]

Iron deficiency anaemia resulted in about one-fifth of maternal deaths and accounted for 0.4% of global total DALYs. In turn, vitamin A and zinc deficiencies were responsible for one million deaths and a combined 9% of global childhood DALYs. In addition iron and iodine deficiencies combined, were responsible for about 0.2% of global childhood DALYs.[5] National prevalence data on micronutrient deficiencies are, however, very limited. Based on the WHO data base, five millions children had night blindness associated with vitamin A deficiency.[3] It was also estimated that the deaths of 20-24% of children who died of measles, diarrhoea and malaria were attributable to vitamin A and zinc deficiencies. Each year, 38 million newborns are at risk of iodine deficiency. Globally, 47% of those under five suffered from anaemia, presumably partly reflecting iron deficiency although parasite infestation also plays a role. In Asia 47.7%, or about 170 millions children, were found to be anaemic.[6]

Role of nutrition in cognitive development and cognitive functions

Human brain development begins shortly after conception with the formation of the neural plate; cell proliferation and migration occurring before birth. Brain growth is almost finalized by the age of five, but its development, including: neurogenesis, synapse formation and myelination continues until late adolescence.[7] The processes occur in stages with the sensorimotor cortex being the first to mature, followed by the parietal and temporal association cortex and finally the prefrontal cortex that is responsible for more complex functioning. Mental and motor skill development reflects the development of the various areas of the brain responsible for these skills. Sensory motor skills develop from birth until the age of 2; preoperational including verbal skills develop between 2-7 years; concrete operational skills between 7-12 years and formal operational skills including logical and systematic reasoning between 12-15 years.[8] The brain requires adequate nutrition for optimum growth, development and maturation. Protein, fatty acids (specifically, long-chain fatty acids) and many micronutrients are essential for the proper structure of brain tissue, healthy neurochemistry, and the overall growth and maturation of the brain. On the other hand, maternal over nutrition may result in per-

manent changes within the central appetite-regulating network in the hypothalamus, predisposing the offspring to obesity.[9] Apart from nutrition, other factors such as poverty, socio-cultural and psycho-social risk factors also influence child development.

Micronutrients and cognition

There is strong evidence for the beneficial effect of iron and iodine supplementation on several aspects of cognitive performance in children who are deficient in these micronutrients. Infants with iron deficiency anaemia exhibited lower cognitive scores, poorer motor development and altered social emotional development.[10] Iron deficiency seems to have long-lasting irreversible effects in children below two years, but may have reversible consequences when it occurs later in childhood.[11,12] Iron is taken up by transferrin receptors in the endothelial cells and its transport through the blood-brain barrier is regulated and depends on iron status.[13] Iron deficiency in infants affects neurogenesis, particularly the formation of the hippocampus and striatum, and the location and function of oligodendrites. Iron deficiency also affects neurochemistry, particularly the production of dopamine.[14] Depending on the stage of brain development, iron deficiency may result in a loss of brain iron that compromises cognitive development.

Thyroid hormones play an important role in neurocellular proliferation, synapse and dendritic formation. Iodine deficiency during pregnancy causes irreversible neurological and cognitive deficits in the child. Maternal hypothyroidism disrupts neuron migration in the foetal brain, causing irreversible structural changes.[15] At 2 years of age the offspring of women with hypothyroidism at 12 weeks of gestation had delayed mental and motor functioning as assessed with the Bayley Scales.[16] When it occurs later in pregnancy, iodine deficiency may cause cretinism – characterized by severe mental and growth retardation. At a later age, iodine deficiency may limit development resulting in lower IQ scores.[17] Cognitive abilities likely to be affected by iodine status are: verbal knowledge, non-verbal and verbal abstract reasoning, visual-spatial perception and executive functioning. Children with a low iodine status perform more poorly on a variety of measures of cognitive performance. In a population with high or severe iodine deficiency, iodine supplementation improved the cognitive performance of iodine-deficient children.[18]

Zinc is essential to the central nervous system and zinc-containing neurons are concentrated in the forebrain.[19] Maternal zinc deficiency can adversely influence foetal brain development. Zinc-dependent enzymes are involved in critical cell replication processes necessary for brain growth, while zinc-finger proteins are important in brain structure; zinc-dependent neurotransmitters in the mossy fibres system of the hippocampus are involved in memory.

B-vitamins play important roles in one-carbon metabolism through the methylation and nucleotide synthesis pathways.[20] Maternal folate deficiency is linked to neural tube defects, delayed intellectual development and other mental disorders in the offspring. Lower maternal folate status in early pregnancy was associated with childhood hyperactivity and peer problems,[21] but had no impact on the neurodevelopment of the offspring at 5 years if the low status occurred in the second half of pregnancy.[22] Case reports of maternal vitamin B-12 deficiency found that the offspring, aged 6 months, showed developmental regression and cerebral atrophy which might be reversed by vitamin B-12 injection.[23]

Provision of multiple micronutrients showed beneficial effects on verbal and non-verbal abilities, including short-term memory, attention and concentration. Meta-analysis of 15 studies of healthy school-aged children found that multiple micronutrients supplementation (most included iron and iodine) improved academic performance and fluid intelligence.[24] In fact given the low cost of micronutrient supplementation and fortification, it has been identified as the most cost-effective solution to help alleviate problems associated with poverty.[25]

Polyunsaturated fatty acids and brain development

Long-chain polyunsaturated fatty acids (LC-PUFAs), especially docosahexaenoic acid (DHA) and arachidonic acid (ARA), are key building blocks in the brain. There is a rapid uptake of DHA and ARA by the infant brain, beginning in the third trimester of pregnancy and continuing throughout the first two years of life.[26] LC-PUFA synthesis is inefficient in both the foetus and young infant, and a supply of preformed LC-PUFAs is necessary to meet the needs of the rapidly developing brain. During pregnancy, LC-PUFAs are actively transported across the placenta. Breast-fed infants continue to receive LC-PUFAs from breast milk that contains all the required fatty acids. However, the DHA supply to the unborn baby during pregnancy, and the DHA content of breast milk, may be low if the maternal diet does not include foods that are sources of preformed DHA.[27-29] However, the supply of preformed LC-PUFAs to both the foetus and the newborn is highly variable.

Several studies have reported no effects of administering LC-PUFA supplements on measures of performance obtained with global tests of infant development, such as the Bayley Scales. However, global tests of infant development were originally designed to detect delayed development, and place undue emphasis on perceptual and motor skills, rather than important cognitive functions: hence, they might not adequately assess cognitive abilities during the first two years of life.[30,31] An alternative approach to the study of the effects of LC-PUFAs on specific cognitive functions is to consider information processing and problem solving. Speed of information processing in infants can be assessed by measures of visual attention (the duration of looking) during visual paired comparison or habituation tests. An observational study reported a significant relation between higher maternal DHA status at delivery, and faster infant information processing on a test of visual habituation at 4 and 6 months.[32] Infants fed a formula supplemented with DHA and ARA showed faster information processing during the first year of life compared to infants fed a control formula.[33] A second approach is means-end problem solving that involves deliberately performing a sequence of actions to achieve a goal. Simple examples include finding a toy that is hidden under a cover, or pulling a cloth to retrieve an out-of-reach toy. Means-end problem solving ability develops

rapidly between 6 and 12 months.[34] Several randomized clinical trials have found that supplementation with LC-PUFAs, especially DHA, during pregnancy and the first six months of life improved problem solving.[35,36] Despite the limited number of follow-up studies, the results have found that the effects of LC-PUFAs on information processing extended beyond infancy to later childhood.[37,38] In contrast, the effects of LC-PUFA supplementation on cognition in older children are less clear. LC-PUFAs have been shown to have both cognitive and behavioural benefits for children with learning difficulties, such as dyslexia or ADHD.[39] In contrast the effect of LC-PUFA supplementation on normal children was limited or even had no effect on cognition and behaviour.[40]

Assessment of cognitive functions in infant and young children

IQ tests have widely been used and provide significant predictions of success in school and related outcomes. However, questions about dietary influences on cognitive development may or not be answered by general IQ scores, and could be most appropriately addressed by using specific age-appropriate cognitive developmental tests that are linked to underlying neural mechanisms. Therefore, an alternative approach to assessing cognitive development in infants and young children is to identify specific aspects of cognition and to develop valid and reliable techniques of measurement.[41]

Early cognitive development should focus on cognitive abilities, namely, memory, attention, language, and knowledge. *Memory* (defined as encoding, storage, and retrieval of information) can be divided on the basis of duration of storage (eg, short term versus long term), type of information stored (eg, semantic - recall of general facts versus episodic - recall of personal events), and accessibility to conscious awareness (eg, explicit versus implicit). Measurement techniques in infants and children include responding to novelty, learning tasks, search tasks, deferred imitation and delayed response. *Attention* refers to the broad array of processes that direct the sensory focus, and can be subdivided into relevant categories. Endogenous attention refers to the internal, volitional process through which sensory focus is directed toward external stimuli and can be contrasted with related aspects of attention (eg, maintaining alertness, orienting toward compelling external stimuli). Endogenous attention can be assessed using laboratory tasks in which the infant or child monitors various stimuli and it is observed how they respond when there is a gap or alternatively overlapping stimuli. Attention is also manifest in a wide array of behaviours so it is amenable to measurement via parent or care giver observation-based reports. Early *language* can be divided into production and comprehension. Multi-word utterances lead to characterizations such as the mean length of utterance and the presence of various levels of syntax and grammar. Language is relatively obvious and thus can be assessed using parental reports, for example the MacArthur-Bates Communicative Development Inventories[42] and various laboratory procedures such as word comprehension. Finally, *knowledge* refers to the content and organization of mental representations. Inferences about the child's knowledge can be drawn from how the child responds to possible versus impossible physical occurrences, organizes and sorts stimuli, and solves problems.

Adaptation of cognitive assessment tools for Asian populations

Cognitive tests of Western origin may prove inadequate when assessing children in developing countries who live in multiple risk environments: nutritional, environmental, socio-economic, although there are also cultural differences. Cognitive test scores should be culturally appropriate; have a consistent construction (they measure the same psychological concept cross-culturally); should be administered in a similar way; care should be taken when translating items to ensure a common meaning.[43]

Three options, adoption, assembly and adaptation, are used to transform an instrument from one culture to another.[44] Adoption of an instrument is used to compare performance on tests across cultures. Assembly involves constructing a new set of measures if the existing tests are inapplicable in another population. Adaptation is a combination of adoption and assembly, hence it involves an accurate translation of the reliable and valid components of the test combined with the substitution of parts that cannot be reliably applied (due to language, culture or psychometric properties).

The Kaufman Assessment Battery for Children (KABC-II)[45] is based on a theoretical model that tries to gain universal validity by minimizing the influence of culture and language.[46] An example was the use of KABC-II with 6-10 year-old Kannada speaking school children of low socio-economic status in Bangalore, India.[47] The adaptation employed an iterative procedure of translating, piloting, and modifying instructions, examples and items.[48] Child psychologists translated the test instructions and items from English to Kannada and the test was independently back translated by a psychologist to ensure consistency of meaning. Information about the children's direct living environment was collected by interviewing parents and teachers. A qualitative judgmental approach was used to pilot test items for cultural appropriateness followed by the use of statistical procedures to assess the reliability and validity of the adaptation. In this exercise, five types of adaptation were needed, namely, 1) construct-driven adaptations related to differences in definitions of psychological concepts across cultures; 2) theory-driven adaptations involving changes required for theoretical reasons; 3) familiarity-driven adaptations based on differential familiarity with the task or item characteristics or stimulus materials; 4) culture-driven adaptations to suit the different cultural norms, values, communication styles, customs, or practices; and 5) language-driven adaptations, the unavailability of semantically equivalent words across languages or from structural differences between languages. Unlike tests of general perception, many non-verbal tests are in fact culturally loaded. Adaptation should also focus on response formats including multiple anchor points. Expertise in linguistic, psychometric and cultural knowledge is indispensable in this adaptation process. As an example, an adapted version of a test was administered to over 500 children[49] and the Cattell-Horn-Carroll (CHC) model[46]

underlying the original KABC-II was largely replicated when tested using a Structural Equality Model. Significant associations were found between test scores, background characteristics (age and gender) and scholastic achievement. Girls performed better than boys in verbal learning recall, verbal fluency, number cancellation time and coding, indicative of better fluid reasoning and the ability to learn tasks. Statistical analysis confirmed that test scores increased significantly with age and the mental processing index (MPI) obtained correlated significantly with arithmetic test results.

Application of knowledge on nutrition and cognition in nutrition studies: Examples from Asia

There are several studies in Indonesia/Australia, India, Thailand and Vietnam on the impact of nutritional intervention on the cognition of children. The NEMO study looked at the effects of a 12-month micronutrient intervention on learning and memory in well-nourished and marginally-nourished school-aged children, aged 6-10 years, in Australia and Indonesia.[50] The parallel randomized controlled trials consisted of four treatment groups of 60 children with: 1) micronutrients (M, containing iron, zinc, folate, vitamin A, B-6, B-12, and C); 2) long chain n-3 fatty acids (FA, consisting of DHA and EPA); 3) micronutrients plus long chain n-3 fatty acids (MFa); and placebo (P) groups. Biochemical status was assessed at baseline and after a 12 month intervention, while school and cognitive performance was measured at baseline, 6 months, and 12 months. In Australia, improved serum ferritin, body iron stores, red blood cell folate, and vitamin B12 were found in the M group. FA treatment also had significant effects on the plasma levels in terms of EPA, DHA, and total n-3 fatty acids. A significant positive effect on their verbal learning and memory (general intelligence and visual attention) was only observed in the M group. Similarly, in Indonesia, supplementation improved micronutrient status and body iron stores. Both the M and FA groups had increased levels of plasma DHA and total plasma n-3 fatty acids. However, in girls but not boys, the M group showed an improvement in verbal learning and memory, although no effect on general intelligence and visual attention was observed. Fatty acid supplementation had no effect on the performance of cognitive tests.

Several nutrition intervention trials and cohort studies in school children were conducted by St John's Research Institute in India. The 'Champion' study compared the effect of two different dosages of a combination of micronutrients and n-3 (omega-3) fatty acids on the growth and cognitive performance of healthy school children from poor socio-economic backgrounds.[51] The four parallel groups received foods fortified with either 100% or 15% of the RDA of micronutrients, in combination with either 900 mg α-linolenic acid plus 100 mg DHA or 140 mg α-linolenic acid for 12 month. Cognitive tests assessing short-term memory, fluid reasoning retrieval ability, cognitive speediness, and overall cognitive performance were conducted at baseline, 6 and 12 months. Over a year in all groups, cognitive test performance improved at a rate about twice that expected. Overall, higher doses of micronutrients were as effective as lower dosages in improving cognitive performance. There was no difference in cognitive performance between the high and low omega-3 fatty acid groups. The Mysore Parthenon birth cohort examined whether lower maternal plasma folate and vitamin B-12 concentrations and higher plasma homocysteine concentrations during pregnancy, were associated with a poorer neurodevelopment of the offspring (long- and short-term memory, reasoning ability, attention and concentration, and visuo-spatial and verbal abilities).[52] The children's cognitive test scores increased by 0.1–0.2 standard deviation per standard deviation increase in maternal folate levels, independent of parental and child demographic factors. There were no consistent associations between maternal vitamin B-12, or homocysteine values, and the child's cognitive performance. While many factors influence the functional outcome of nutritional intervention in children, baseline nutritional status and home environment are particularly critical. The timing, dose and duration of the intervention and the appropriateness of the test also need to be considered when examining the impact of nutrition on the cognition of children.

The Institute of Nutrition Mahidol University has also examined micronutrient intervention in children and pregnant women. Multi-micronutrient-fortified seasoning powder (1/3 of the Thai RDA of vitamin A, iron, iodine and zinc) was fed to school children for 32 weeks and resulted in a significant improvement in iodine and zinc status, as well as reduced respiratory-related illness and diarrhoea. The fortified group performed better on a visual recall task but not the digit span test.[53] A second randomized controlled trial evaluated the efficacy of multi-micronutrient-fortified biscuits, with or without deworming, on the micronutrient status and cognitive performance of Vietnamese school children.[54] The fortification significantly improved serum ferritin, retinol, zinc and iodine status and enhanced the efficacy of deworming. Multi-micronutrient fortification significantly improved forward digit span and Raven's Coloured Progressive Matrices tests (CPM), especially in anaemic children. In a rural northeast area, at 9 years old, there was no significant difference on any of the cognitive outcomes (IQ, Raven's CPM scores) of children who had received iron, zinc, combined iron and zinc, or placebo during their infancy. Growth in both early and late infancy was positively associated with intelligence (full scale, verbal, and performance IQ) at 9 years.[55]

Lessons learnt from these experiences include the following. There have been difficulties in deciding which cognitive tests would be appropriate when using a multiple micronutrient supplement as the intervention. It was not possible to tease out the relative contribution of each of the nutrients on cognitive improvement when the intervention included many micronutrients. In addition synergistic interactions between nutrients cannot be established. Tests such as Wechsler's Intelligence Scale for Children III (WISC III) or Raven Progressive Coloured Matrices have been widely used since they are non-verbal, can be translated and have been validated. However, when using these tests with children who may not be exposed to the same environment as those in urban, more economically advantaged settings, lower scores may re-

flect environmental factors rather than actual cognitive ability.

NUTRITION, BRAIN NEURODEGENERATION AND COGNITIVE DECLINE IN OLDER ADULTS

Neurobiology of cognitive decline and dementia

Brain atrophy associated with ageing proceeds over many decades beginning in young adulthood. The associated cognitive decline accelerates in old age, but there is much variation in the rate of decline, reflecting the individual's 'cognitive reserve', the capacity of the brain to deal with the effects of disease without manifesting clinical symptoms. Also, distinct cognitive functions such as semantic memory are relatively spared by aging, but prospective and episodic memory in particular decline over time.[56,57]

Cognitive decline and functional disability are clinical symptoms of dementia, a series of syndromes that reflect damaged and malfunctioning neurons. The most common, Alzheimer's disease (AD), accounts for between 50-70% of all dementias, with vascular dementia accounting for another 10-15%, although a considerable proportion have cerebrovascular pathologies, so-called mixed dementia. There are as many as fifty other causes that include head injury, drugs, alcohol, and specific nutritional deficiencies. Although the most widely recognized symptom of AD is memory loss, other mental functions including mood and language are also impaired. To date, therapies developed for AD provide non-lasting symptom alleviation, but they do not reverse or prevent the progression of disease.

The accumulation of neuritic plaques (ß-amyloid) and neurofibrillary tangles (aggregates of the cytoskeletal tau protein) are considered the histopathological hallmarks of AD, and such changes are known to precede the onset of AD by decades. Factors including oxidative stress and inflammation are known to play important roles in the ageing of the brain and hence cognitive decline. For example, oxidative DNA damage is shown to reduce the expression of selectively vulnerable genes involved in learning, memory and neuronal survival, accelerating brain ageing and cognitive decline in middle age,[58] and has been shown to occur in individuals with mild cognitive impairment (MCI) and AD.[59] Buccal cells of AD patients have shorter telomeres, components essential for chromosomal stability, and telomere shortening has been linked to accelerated senescence.[60]

Role of nutrition in CNS neurodegeneration and cognitive decline

Given the limited effectiveness of current pharmacological products, there is an emerging interest in developing therapeutic nutritional products ("neutraceuticals") for dementia. Nutrition may modulate cognitive processing at many levels through multiple cell signalling pathways and various modes of action such as synaptic strengthening, neuro-protection, the facilitated release of neurotransmitters, vasodilation, modulation of neurotransmitters (glutamate, acetylcholine, 5-HT, dopamine and GABA) receptor systems, and inhibition of acetylcholinesterase activity. At the cellular level, nutrient deficiencies may result in DNA damage, reduced regenerative potential, demyelination and brain atrophy.[61] For example, nutrients such as folate and vitamin B-12 are required for genome maintenance, and iron or copper overload can exacerbate homeostatic imbalance in redox pathways.[62] Malnutrition is common in the elderly,[63] and marginal or biochemical deficiencies in micronutrients have been shown to have significant health effects.

Neutraceutical product development typically starts with the screening of functional ingredients for their effects on key underlying biological mechanisms associated with cognition. A potential ingredient is selected and molecular studies delineate their mode of action and efficacy using animal models, before moving to clinical trials. The potential of nutritional products to slow cognitive decline and dementia is demonstrated by a rapidly growing body of evidence. A review of the evidence suggested that a range of dietary and nutritional factors are associated with a reduced risk of cognitive decline and AD: they included vitamin E (from food), folate and vitamin B-12 (from food and supplements), fish at least once per week, ω-3 fatty acids, a moderate intake of wine (1-6 drinks/week), consumption of fruit juices, less calories and saturated fat, and a Mediterranean type diet.[61]

Folate and B-12

The evidence is compelling for a link between vitamin B-12, folate and cognitive functioning.[61] Folate and B-12 are intimately involved in methylation and DNA/RNA reactions that are critical in the biosynthesis of nucleotides, membrane phospholipids and monoamine neurotransmitters in the brain. As folate provides the methyl group for the conversion of methionine to S-adenosylmethionine (SAM), the major methyl donor for methyltransferase reactions, CNS hypomethylation is a key biochemical defect in impaired brain functioning resulting from folate deficiency.[64] Low vitamin B-12, folate and high homocysteine status are associated with higher DNA damage and shorter telomeres in older men.[65] Among non-demented older adults in the Singapore Longitudinal Ageing Studies cohort, low levels of serum folate were associated with poorer performance on tests of memory, learning and language. High levels of homocysteine, independently of folate, were associated with deficits in constructional ability and processing speed,[66] and were also associated with a smaller cerebral white matter volume. A study in Malaysia also showed the association between cognitive impairment and poor serum folate concentration and DNA damage.[67]

Nutrient-gene interaction as well as epigenetic factors may also impact on cognitive functioning. For example, MTHFR gene polymorphisms in the folate pathway are linked to susceptibility to AD.[68] The association between serum B-12 and global cognitive function, episodic memory and attention/working memory was significantly more pronounced in individuals with the APOE-e4 genotype, suggesting a greater susceptibility to the influence of variations in the level of vitamin B-12.[69]

Long chain polyunsaturated fatty acids

The long chain omega-3 polyunsaturated fatty acids (n-3 PUFAs) eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3) are found in high levels in the brain, with DHA being particularly found in high concentrations in deep brain structures.[70] Due to the

inefficient synthesis of DHA from its precursor α-linolenic acid (ALA, C18:3n-3), a supply of preformed DHA from food sources such as fish and shellfish is essential.

Cell culture and animal models provide mechanistic support for a possible clinical benefit of DHA in AD. n-3 PUFA may influence neural functioning through its effects on proteins/enzymes that play a role in brain membranes,[71] neuronal gene expression,[72] and as a precursor of the lipoxygenase product (neuroprotectin D1) which promotes resolution of inflammation: together eliciting potent cell-protective, anti-inflammatory and prosurvival repair signalling.[73] DHA may also promote neuronal survival via the brain derived neurotrophic factor and other signalling pathways.[74] It also attenuates zinc transporter expression and reduces zinc influx into neuronal cells.[75] Finally, the neuroprotection of n-3 PUFA may be attributed to its role in blood vessel dilation and improved blood flow.[76] Cell culture and transgenic animal models suggested that DHA supplementation attenuates amyloid and dendritic pathology in AD.[77,78] Post-mortem studies have found lower DHA concentrations in the brains of AD patients.[79]

Epidemiologic studies examining n-3 PUFA intake in food, or the examination of blood levels, also support a possible beneficial role for DHA in AD. Among 11 prospective, 3 cross-sectional studies and one case-control study that examined n-3 PUFA status (dietary intake or blood levels) and the risk of developing AD, one study showed a positive relationship between plasma phospholipid levels and risk of AD, while 2 studies demonstrated no significant effect, and 12 studies reported an inverse relationship between AD risk and n-3 PUFA status.[80]

Clinical trials of n-3 PUFA supplementation are limited in number and vary in the study population, dosage, preparation, and exposure duration. The outcomes also vary. Evidence of a therapeutic effect in patients with AD is lacking, but the results suggest that DHA may benefit patients with MCI or healthy older adults with mild cognitive deficits. A recent DHA supplementation study showed improved learning and memory functioning in healthy subjects with age-related cognitive decline.[81] A smaller study showed improvement in immediate verbal recall with phosphatidylserine (containing omega-3 fatty acids) supplementation.[82] However, larger randomized clinical trials are needed before firm conclusions can be drawn.

Amino acids and proteins

Proteins and amino acids play important biochemical roles in cognition as key component of brain cells. In the brain, proteins function as receptors, ion channels and transport mechanisms, and about half a dozen amino acids function as promoters or precursors of neurotransmitter synthesis. Tryptophan is an essential building block for serotonin whereas phenylalanine and tyrosine are building blocks for dopamine, epinephrine and norepinephrine, and glutamine/glutamic acid is a building block of gamma-amino butyric acid (GABA). It has been considered whether dietary amino acids and proteins are capable of affecting cognitive functioning by influencing the availability of these substrates.

There is, however, limited evidence to support any clinical effects of providing amino acids and peptides. The cognitive effects measured in generally well-fed and healthy populations have been unconvincing, and often contradictory. Under normal conditions, dietary intake has little/no effect on synaptic amino acid pools.[83] However, in abnormal situations when regulatory controls are disrupted, dietary amino acids may be influential.[84,85] Increasing evidence suggests possible cognitive benefits from consuming very short peptides, such as carnosine, which is naturally present in the human brain and readily passes through the blood-brain barrier. A possible neuroprotective and anti-AD property of carnosine has been suggested[86,87] by its ability to detoxify advanced glycation end products that may otherwise alter neural structures and facilitate pathological neuro-degeneration.[88]

Functional food ingredients and herbal substances

As cognition involves multiple processes, interacting in complex and possibly idiosyncratic ways, it may not be surprising that single agents have little impact on cognitive decline and dementia. Unlike mainstream pharmacological agents, nutraceuticals and herbal medicines - 'nutra' - typically contain dozens of active *phytochemicals*. It is possible that by acting in concert on multiple systems (neuronal, metabolic and hormonal), 'nutra' agents may offer a promising approach. Since behavioural processes are themselves modulated by multiple systems, the effects of herbal extracts may particularly depend upon complex interactions within and between biological systems.

The plant polyphenols in tea *(Camellia sinensis)* are catechins, including epigallocatechin gallate (EGCG) in fresh green tea, and their oxidized polyphenolic compounds, theaflavins and thearubigins, formed during fermentation in black tea (fully fermented) and Oolong tea (semi-fermented). The well known anti-oxidant properties of tea polyphenols are not altered by fermentation.[89] The neuroprotective effect associated with EGCG may be attributed to its antioxidant and iron-chelating properties, in addition to modulating cell signalling and cell survival pathways.[90,91] As well, EGCG has been shown to reduce Aβ generation by promoting α–secretase cleavage of amyloid precursor protein (APP),[92] and both black tea and green tea inhibit human acetylcholinesterase activity.[93] Other phytochemicals such as theanine, which is an amino acid uniquely found in tea leaves, also show neuroprotective effects.[94] Recent epidemiological studies in elderly populations in the Japanese Tsurugaya Project[95] and the Singapore Longitudinal Ageing Studies[96] have observed that a higher consumption of green, black and oolong tea was associated with a lower prevalence of cognitive impairment and decline, as well as better performance on several tests of cognitive functioning, effects not similarly observed with coffee drinking**.**

Blueberries, walnuts or other fruits and vegetables that are rich in phytochemicals have been shown in animal models to slow or reverse deficits in spatial memory and learning.[97] The mixture of polyphenols may have a synergistic reaction, as fractions of the blueberry polyphenols are less effective than blueberry juice. Brain localization studies have shown that anthocyanins are able to pass

through the blood-brain barrier and become localized within the brain in areas such as the hippocampus, frontal cortex and striatum that are important for learning and memory. The anthocyanins level in the brain has also been associated with cognitive performance.[98] Dietary supplementation with blueberry appears to promote hippocampal neurogenesis by increased dendritic growth,[99] while walnut supplementation appears to increase resistance to oxidative stress and inflammation by decreasing the number of activated microglia in the aged hippocampus. Preliminary clinical data in humans suggested that blueberry supplementation improved verbal memory and word list recall in older adults with an early onset memory decline.[100]

Found in curry spice (turmeric), curcumins have strong anti-inflammatory and anti-oxidant properties. Recent experimental studies have shown that curcumins in the diet reduce plague deposits in the brains of transgenic AD mice.[101] In the Singapore Longitudinal Aging Studies subjects, regular curry intake was found to be associated with better cognitive performance.[102] There remains a need for randomized controlled trials to generate definitive evidence to support the beneficial effects of nutritional factors in preventing dementia.

Functional MRI studies showed that flavonoid-rich cocoa intake increased localized brain activation in the dorsolateral prefrontal cortex, anterior cingulate and parietal cortex, coinciding with peak serum flavanol, although there was no improvement in task performance.[103] Cross-sectional epidemiological data suggested that a diet high in cocoa is associated with better cognitive abilities,[104] but a randomized controlled trial of the short-term (6 weeks) effects of dark chocolate and cocoa failed to show a beneficial effect on neuropsychological functioning.[105]

Panax ginseng

Both laboratory and clinical studies strongly suggest that Panax ginseng may have beneficial effects on cognitive performance. Recent evidence demonstrated that Panax ginseng can directly modulate neuronal activity as evidenced by the improvement in the electroencephalograph (EEG) profile.[106] Randomized controlled trials with heterogeneous outcome measures, trial duration, and ginseng dosage, suggested improvements in working memory, behaviour and quality of life.[107,108]

Salvia (sage) is recognized in Ayurvedic, Chinese and European medicine as having beneficial effects on the brain, nerves and memory. Besides its anticholinesterase properties, salvia shows anti-oxidant, pro-oestrogenic and anti-inflammatory properties. A small number of trials using extracts of S. lavandulaefolia and S. officinalis have shown improved memory and attention in healthy older volunteers,[109] and in patients with mild to moderate AD.[110]

Methodological issues in clinical trials of nutrition and cognition in older persons

The fact that age-related cognitive decline is known to vary widely among individuals, and take place over an extended period from early in life, has important implications for experimental designs. A preponderance of evidence thus rests on epidemiological data that must meet a range of strict criteria to demonstrate causality. The absolutely essential criterion is that exposure must preceded the outcome. Causality is more likely if the relationship is strong; there is a dose-response relationship; results have been replicated in different settings using different methods; the suggested effects are plausible and agree with accepted understandings of pathology; and finally, alternative hypotheses have been ruled out.

Information from randomized, double-blind, placebo controlled studies, nevertheless, is highly desirable given their ability to establish causality. Large samples and long-term studies are required, especially if gross outcomes such as a clinical diagnosis of dementia or global cognitive performance such as the Mini Mental State Examination (MMSE) are used. In this regard, more sensitive cognitive tests that selectively measure specific domains of cognitive functioning are expected to better track subtle changes over relatively shorter time periods. Usually, it is necessary to employ a range of tests carefully selected for their validity, sensitivity, level of difficulty, reliability and ease of administration.

Each study thus calls for a customized approach, taking into account the specific aims (what needs to be substantiated), product characteristics (what seems appropriate to measure?) and target population (what is feasible to measure?).[111] There is no "one size fits all" battery of cognitive tests, and even "off-the-shelf" assessment tools need to be tailored to the target groups. Attention to test planning and administration that takes into account standardization of procedures, minimizing confounding factors, such as subject's mental state and the testing environment, potential learning and practice effects, have an important impact on the quality of the data. The evaluation of effect specificity, interaction between cognitive domains, speed-accuracy trade off, time on task(s) and/or test(s) and the potential role of compensatory effort (increased effort to cope with less efficient brain functioning) contribute to the correct interpretation of the effect of the nutritional intervention on cognitive functioning. An interdisciplinary approach from diverse perspectives of behavioural, nutritional and biological sciences is vital for credible results.

The alternative approach to measuring cognitive decline is to use a biomarker that detects a neuropathological feature with a proven relationship to neuropathologically confirmed AD cases, that is reliable, non-invasive, simple to perform and inexpensive.[112] As cognitive aging involves various biological mechanisms such as oxidative stress, inflammation, homocysteine and advanced glycation end products that can be modified by nutritional factors, such biomarkers of cognitive ageing may be useful to measure a cognitive response to dietary or nutritional interventions. As a case in point, beta-amyloid and Tau protein measurements in cerebrospinal fluid are currently recommended, but are invasive and not acceptable to all participants.

Another approach is to use brain imaging techniques for global or regional volumetric measurements, such as of the hippocampus and entorhinal cortex that are known to be associated with mild cognitive impairment (amnestic MCI) and early AD.[112] Brain imaging techniques using

Pittsburgh Compound B (PiB) may be used to measure β-Amyloid deposition, a hallmark of AD pathology.[112] However, the known inconsistency between biological measures and clinical symptoms should be noted; at post-mortem individuals with extensive AD pathology may display few or no symptoms before death.[113] However, in the Australian Imaging, Biomarker and Lifestyle (AIBL) Flagship Study of Ageing, a positive PiB scan indicating high Aβ burden was present in 67% and 98% of MCI and AD participants, respectively.[114] However, high Aβ burden was also found in 31% of healthy controls although the percentage increased with age; 18% of healthy controls aged 60-69 had high PiB binding, rising to 65% in those over 80 years. A positive PiB scan in persons with MCI is the strongest predictor for cognitive decline and conversion to AD;[112] 46% of MCI cases with positive PiB status at baseline converted to AD, as compared to 16% in negative PiB subjects. Altogether, a combination of imaging measures and biomarkers that are translatable into behavioural effects may be necessary.

The heterogeneity of the nutritional interventions and measured endpoints is an important consideration. Dementia is a symptom that may reflect many different diseases, such that different aetiologies mean that nutritional intervention will impact in different ways in different individuals. For example because the Wernicke-Korsakoff syndrome responds to thiamine supplementation, and vitamin B12 deficiency responds to supplementation of this vitamin, does not imply similar benefits occur for other forms of dementia.

With some products experience showing that many cognitive effects are dose dependent, but the highest dose does not necessarily provide the greatest effectiveness. Complex dose-time-task interactions, and the dissociation of acute versus chronic effects, need to be addressed with the appropriate methodology. In interventions involving herbal extracts, it is important that the extract is standardized and well characterized for findings to be reproducible. The underlying mechanistic link will need to be investigated using biomarkers and the examination of receptor and enzyme functioning.

With regards to the target population a potentially fruitful way of increasing sensitivity is to study those who are at increased risk of developing dementia, such as those with genetic polymorphisms (particularly the APOE-e4 allele), lifestyle, behavioural and cardio-metabolic risk, or are displaying early symptoms (such individuals with MCI). A criticism of this approach is that these individuals may have already minor brain degeneration and arguably nutritional intervention studies should aim at preventing rather than treating cognitive decline, studying those of a younger age whose brain functioning can still be modulated. Further investigations with other genes and gene-nutrient interactions are needed.

Given the historical use of many functional ingredients in Ayurvedic or traditional Chinese medicine, Asia offers a boundless potential for investigating a role for novel nutritional interventions in cognitive functioning. More information, however, needs to be established concerning these natural ingredients, especially with regards to their toxicity, safety and clinical efficacy. Nutritional product development needs to address challenges in identifying and targeting the multiple pathways stimulated by individual active components, as well as the complex interaction between multiple components found in these natural products. There is also a need to demonstrate clinical safety and efficacy for specific populations, together with product stability, palatability, packaging and affordability.

There are pertinent considerations for conducting nutritional and cognitive research in Asia. There should be careful understanding of the socioeconomic and education background of the population of interest. With regards to the use of MMSE for assessing global cognitive performance, unique differences in MMSE scores have been shown among Chinese, Malays and Indians, and by educational level among older Singaporeans.[115] Thus, stratification by education and ethnicity should be part of the study design. Similarly variations by gender or education may or may not be present for particular cognitive tests: such difference should be explored in initial studies.

EVIDENCE-BASED CLAIMS AND CONSUMER UNDERSTANDING

It is important that the evidence on the role of nutrition on cognitive functioning is clearly communicated to the general public. One way is the use of a health claim, which is intended to provide factual information of health related properties of certain foods, nutrients and bioactive substances, for the purpose of guiding the consumer to make healthy food choices. A claim needs to be both scientifically defensible and able to communicate the intended meaning to the general public. In turn regulators require appropriate and substantial evidence for claims in the area of nutrition and cognition that are specific, quantifiable and related to specific target groups.

The current status of health claims in the area of nutrition and cognition in various regions of the world are considered. Topics covered include the existing regulatory framework, the review and substantiation process, and the evidence required. The industrial perspective is discussed using the role of docosahexaenoic acid (DHA) for cognitive development as a case study. The consumers understanding of the role of nutrition in cognitive functioning is also examined as the nature of the consumer understanding should be taken into account when examining such claims. It is important to ensure that the wordings of the claims are correctly understood by consumers.

European perspective

In December 2006, the European Union adopted a new regulation concerning nutrition and health claims made about foods. Article 13.1 of the regulation refers to 'general function' health claims, which includes psychological and behavioural functions.[116] Article 14 of the regulation refers to claims involving disease risk reduction, child development or health.[117] The European Food Safety Authority (EFSA) is responsible for verifying the scientific substantiation of submitted claims.

Claims submitted under Article 13.1 have a format which specifies the food constituent (eg Vitamin B-12, Tryptophan), the health relationship that is the subject of the claim (eg 'cognitive function', 'attention'), proposed wording for the claim (eg 'improves concentration', 'enhances memory'), conditions of use (eg 'food supplement

with 75-225 mg in the daily dose'), and target population. The submitted claim must provide a list of scientific articles to support the claim.

Under the EFSA panel, the working sub-group for mental and nervous system claims developed the methods and procedures for reviewing claims involving psychological, behavioural and neurological functioning. The protocol involves: initial screening to establish whether a claim meets the basic criteria for review; assessing whether the claimed effect is beneficial to human health; identification of the target population; and evaluation of the scientific evidence.

There are several steps in the initial screening protocol. First, the food constituent needs to be adequately characterized; this would be a challenge in the case of herb extracts containing unspecified substances. Second, the health relationship defined in the context of proposed wording must be meaningful and measurable. Claimed effect on memory, attention/concentration and resistance to stress would meet these criteria while general terms such as cognitive functioning or mental performance would be too vague and cannot be specifically measured. Third, the conditions of use of the food constituent must be adequately specified (e.g. quantity required to achieve the claimed effect). And lastly, there must be scientific evidence obtained from human studies. Only applications that pass the initial screening are reviewed.

Assessment is also made as to whether the claimed effect is beneficial to human health. The majority of claimed effects (eg improving memory) are beneficial, but others may not be, for example, the enhancement of alertness/arousal might not be beneficial if it reaches a position of being perceived as anxiety. Target populations also need to be identified. When it is not specified, the target population is assumed to be the general healthy population.

Australian perspective

Food Standards Australia New Zealand (FSANZ) is currently working on a new health claims standard which will regulate nutrition content claims (statements about the presence or absence of a nutrient, energy or a biologically active substance in the food), general level health claims (claims about the effect of a nutrient or substance in a food on a health function or a non-serious disease), and high level health claims (claims about the effect of a nutrient or substance in a food, that make reference to a serious disease or biomarker of a serious disease).[118] Claims will have to be scientifically substantiated and not misleading. Meanwhile, health claims are currently regulated by a transitional Standard 1.1A.2; under this standard, the only health claim that can be made about a serious disease is a claim on the benefit of maternal folate consumption in reducing the risk of having a baby with a neural tube defect.[119]

Maintaining functional capacity is essential over the life course, beginning with optimal growth and development, maintaining the highest possible level of functioning in midlife and finally preventing disability and maintaining independence in older life.[120] Scientific substantiation using peripheral approaches has been used in a number of cases, for example, in the development of dietary strategies to reduce cholesterol. We can learn from this type of approach when studying the role of nutrition in the brain, whether for sustenance or in a disease state.

Some understanding of the relation between nutrition and lifestyle and the brain has been provided by the Australian Imaging, Biomarkers and Lifestyle (AIBL) Flagship Study of Ageing. In addition, a systematic review on diet, physical activity, mental activity and social engagement in the prevention of dementia that is being undertaken and headed by CSIRO Preventative Health Flagship in Australia, will be able to provide insights. The findings of a review of traditional herbal medicine for dementia has been published.[121]

Understanding the pathology of AD also provides useful information. The amyloid hypothesis postulates that amyloid beta (Aβ) deposits are the fundamental cause of AD.[122] Fragmentation of Amyloid precursor protein (APP) produces mis-folded peptides that form into sheets that eventually aggregate to form fibrils, the accumulation of which create plaques. Intervention is potentially possible at several stages of this pathway: secretase inhibitors prevent amyloid production; plaque formation inhibitors prevent amyloid aggregation; amyloid clearance promoters; anti inflammatory compounds or antioxidant alleviate neural toxicity. Some of the known fibril inhibitors and distruptors are epigallocatechin-3-gallate (EGCG), curcumin, resveratrol and melatonin. They generally possess phenolic structures and may have the potential to inhibit the formation of amyloid fibrils.

Another important aspect of scientific substantiation would be the ability to monitor amyloid fibril formation. Real time monitoring of the fibril formation has been possible using Thioflavin T as ThT binds to amyloid fibrils and enhances its fluorescence emission.[123] Screening of food/plant extracts for potential Aβ fibril inhibitor/ disruptor properties is also possible using TEM imaging to examine whether extracts could prevent Aβ42 fibrillogenesis and oligomerization or the disaggregation of preformed Aβ42 fibrils.[124]

Japan perspective

In Japan the function of food is divided into nutritional functions (primary), sensory functions (secondary) and psychological functions (tertiary). A functional food is defined as one with a tertiary function. In 1991, a regulation on Foods for Specified Health Uses (FOSHU) was established. Under a revision of the system in 2005, foods with health claims consisted of those concerning nutrients (involving 12 vitamins and 5 minerals) and FOSHU. The latter in turn is made up of standardized FOSHU, qualified FOSHU and disease risk reduction claims. The number of approved FOSHU products increased to a total of approximately 1,000 in September of 2010.

The existing FOSHU can be categorized into eight groups according to the health claim, including gastrointestinal conditions, blood pressure, serum cholesterol, blood glucose, the absorption of minerals, blood fat levels, tooth and bone health. An approval system has been in place to systematically evaluate each application by an expert committee under the Consumer Affair Agency and Food Safety Commission. The requirements of the Japanese FOSHU approval system are basically similar to

those of the Codex guidelines and to the regulations on the substantiation of health claims in the EU and US. The main criteria include: health claims should primarily be based on evidence provided by well-designed human intervention studies; the totality of the evidence should be identified and reviewed; effective components should be characterized by appropriate methods.

There are currently no FOSHU claims relating to cognitive functioning. Some possible reasons for difficulties in obtaining such approvals include: a lack of agreement of the meaning of a measure and the measurement process**,** the consistency of the health claim wording with the results of human studies and the magnitude of any differences from the placebo. Cognitive function-related topics under study by Japanese researchers include the prevention of memory loss (eg effects of DHA on cognitive function in elderly people), improvement of sleep quality (eg effect of glycine on sleep in healthy people), and recovery from fatigue. Such claims could come under the category of improving physiological function and organ functioning or causing short-term changes in bodily functioning.

Southeast Asia region perspective

There is considerable interest amongst health professionals and the food industry in the Southeast Asia Region in making health claims related to the ability of nutrients and other food components to improve mental or cognitive performance, learning capability and brain growth and development. This is evident from media articles, advertorials and advertisements dealing with such "functional" claims. The nutrients or food components involved include several polyunsaturated fatty acids (especially DHA and AA), sialic acid, tryptophan, taurine, phospholipids, iron, choline, zinc, "antioxidants", and even proprietary components. These claims are targeted mainly at children but also mention adults. The lack of enforcement of regulations related to unsubstantiated claims, especially those in advertisements, is a concern that needs to be addressed.

There are few officially approved health claims in the Southeast Asia region.[125] Malaysia has only one approved "function" claim: "sialic acid is an important component of brain tissue". This claim is only permitted for use in infant formula and follow-up formula. Singapore also has a few functional claims related to foods for infants and young children: "choline helps support overall mental functioning", "DHA, AA are important building blocks for development of the brain and eyes in infant" and "taurine helps to support overall mental and physical development". Nevertheless, most authorities in the region do provide opportunities for the food industry to apply for functional claims that relate nutrition and cognitive functioning. There are processes and systems in place to allow the review of such applications by relevant experts appointed by the authorities. Information required to be submitted include the proposed wordings of the intended claim and its scientific substantiation. The proposed wordings of the intended claims have to be specific, clear and focused. Catchy wordings that attract consumers may be too broad and difficult to measure. Data to support the claim should preferably be from human intervention trials. The intended claims must be measurable using specific parameters. The proposed claim wordings must be based on, and match, findings obtained from scientific studies.

Methodologies used to provide substantiation must be appropriate for the intended claim. Methodologies for measuring mental and cognitive performance are particularly challenging and have to be socio-culturally appropriate for the population to which the product is directed. In addition, in the case of specific nutrients or food components that are not in the current permitted lists, applications have first to be approved to allow the use of such ingredients.

Industry perspective – DHA as a case study

DHA is a nutritional product investigated for over a decade for its potential importance in cognitive development. Pure forms of DHA have been developed, on a large scale, through fermentation processes using micro-fungi and marine algae, and are used for various purposes including inclusion in infant formula. Clinical trials have been conducted around the world to establish the efficacy of DHA.

A review of 873 brain-platform global new products showed a significant number of them included DHA (36.2%), taurine (25.8%), choline (25%), and omega 3 (7.1%) in their formulation.[126] Building the case for the addition of DHA to infant formula for the development of the central nervous system has not been easy. Human requirement for DHA has only been established recently. Educating the consumer takes time and is often confounded by misleading messages. Awareness of the suggested benefits of DHA varies with different countries with China and Japan being most aware. DHA is mostly linked to heart health and less to eye and brain functioning. There is, however, recognition that diets deficient in DHA will have an impact on cognitive abilities.[127]

There are several reasons for the addition of DHA to infant formula. DHA is found in human breast milk at varying levels.[29] The WHO/FAO agreed that it has convincing evidence of benefits for brain and visual development in infants.[128] DHA has been recommended for pregnancy and during lactation by health authorities in England, France, Netherland, Australia, and the US Institute of Medicine. During gestation, DHA is preferentially transferred across the placenta to the developing foetus. The presence of DHA in breast milk is often cited as a possible reason why breast fed babies have better cognitive functioning than those fed with a formula without DHA.[129] A consensus statement suggested that pregnant and lactating women should have an average dietary intake of at least 200 mg DHA/day.[130] No DHA supplementation studies of infant and children have reported adverse effects on development and cognition. With regards to maximum intake, a cohort study showed that consuming 1 – 7.5 g/day of DHA had no adverse response.[131]

The USA has authorized "Structure/Function" claims for DHA. For most of the world, the obligation is on the manufacturer to be able to back up any on-pack claim. the European Food Safety Authority has given positive opinions on DHA in relation to the maintenance of normal brain function under Article 13; in order to bear the claim foods should contain 250 mg of DHA in one or more servings.[132] For a claim related to brain development it is

considered in relation to child development under Article 14, but EFSA opinions to date have been inconsistent.

Consumer understanding

There is a dearth of studies of consumer perceptions of the association between nutrients in specific foods or in supplements and brain health, cognition or mental alertness. Available data are limited to a few examples at different life stages.

In pregnancy, folic acid has been linked to neural tube defects (NTD). A survey on the knowledge and use of folic acid among 300 Irish women attending ante-natal clinics showed that 92% of respondents had heard of folic acid, whereas 67% knew it could prevent NTD; 30% had been advised to take it around conception but overall only 18% did. [133] A similar survey among 300 UK women also showed that 91% of respondents knew folic acid could prevent NTD but only 44% took it around conception; knowledge about the correct timing of folic acid intake was seen in 76%.[134] It is apparent that folic acid awareness has not been accompanied by a corresponding increase in its consumption. In the US, a survey showed that 61% were aware of the association between folic acid consumption and a reduced risk of brain damage/NTD, although only 37% of respondents consumed and 43% expressed a likelihood of consuming folic acid.[135]

A US survey also showed that 72% of respondents agreed that specific foods or beverages can improve mental performance.[135] Using caffeine as an example, when asked the reason for consuming caffeinated food/ beverages, most participants (58%) consumed them for the taste; to stay awake/wake up (50%) and to increase concentration (10%). They also agreed that caffeine helped to stay awake/wake up (61%), increased energy (49%), improved mental performance (28%) and reduced the risk of brain and/or nerve disease such as AD or Parkinson's disease (11%).[136] In the case of omega-3, 72% were aware of an association between omega-3 consumption and cognitive development with 46% currently consuming and 42% expressing a likelihood of consumption.

Among Europeans, labels were important as a source of nutritional information. Participants also indicated that magazine/news articles played an important role in addition to health related materials. In the USA, the most influential source of information is the health professional (52%), followed by a dietitian (36%), health association (28%), food label (23%) and internet (20%).[135] Looking at the information available online, a quick analysis of the first 30 websites found in response to the term "brain food", produced the following list in descending order of the frequency of being mentioned: nuts, salmon, berries, flax seeds, eggs, leafy green vegetables, whole grain, cocoa, green tea, and coffee. While there is no guarantee of the accuracy of information available online, many consumers refer to it.

A survey of consumer responses to labelling health information in China and Malaysia showed that consumers were motivated by short term benefits and had limited understanding that the impact on health of food choice is generally long term and cumulative. They also did not distinguish between nutrition/health information based on scientific evaluation and traditional folk wisdom.[137] Educational institutions, medical practitioners and other channels such as the internet, TV, radio, newspapers and word of mouth were reported as information sources for both traditional and scientifically substantiated food-health associations. In summary there is very little consumer insight into the relationship between nutrition and cognitive functioning.

DISCUSSION

Cognitive testing

Those unfamiliar with cognitive testing sometimes hope for a standard test battery that can be used universally. It is unfortunately a largely unrealistic request. Anybody who looks for an analogy between cognitive testing and for example a biochemical assay fails to understand the nature of psychological functioning. One can reasonably expect that given the same conditions of substrate, temperature, pH and other relevant parameters, within measurement error a biological assay will generate reproducible results. In contrast no two samples of human beings will be the same, and no one sample will be the same on two occasions. It should, however, prove possible to produce reproducible findings when large enough groups are considered and obtained from similar populations, although the results will be an average of a population rather than a statement about any individual. Even this assumption assumes that we understand all the variables that influence a particular aspect of the human condition and we can therefore specify the nature of the population. Human behaviour reflects a lifetime's individual experiences that vary on a multitude of dimensions, many of which are difficult to measure retrospectively and about which we are unlikely to be aware in many instances.

Cognitive functions have been categorized as falling in six main areas: executive functioning, memory, attention, perception, psychomotor and language skills. In turn, each of these domains can be subdivided. In addition the performance of each will reflect motivation, mood, fatigue and factors such as the time of day as functioning is influenced by circadian rhythms. Tests need to be tailored to the population being studied. A particular test may be so difficult that almost nobody is able to get more than a few correct answers. Motivation can suffer so that the performance on unrelated tests also declines. Equally a test can be so easy that most approach maximum scores and therefore there is an inability to distinguish performance. When considering dementia there is a particular problem in that ability changes with the stage of the disease: as such many forms of a test will be required that reflect the degree of pathology. Similarly with children cognitive capacity changes with age, such that a range of tests will be required if they are monitored over several years, or a sample contains children of a range of ages.

Although cognitive tests attempt to measure only one aspect of cognition, the integrated nature of human functioning ensures that this can never be fully achieved. For example a test of memory inevitably also reflects perception, attention, mood, motivation and depending on the task may also use language skills and strategic planning. Any study of a nutritional intervention that uses only one cognitive test will inevitably be unable to establish whether any significant difference on, for example a

memory test, reflects memory as such, rather than an inability to sustain attention, motivation or mood. It is surprising that many very expensive large scale and long term trials have failed to give the attention required to understand the nature of any cognitive changes. Because the test is categorized as a test of memory it cannot be assumed that any difference necessarily reflects a change in memory as such. Only a battery of well chosen tests will allow the profile of changes in cognitive functioning to be interpreted.

An illustration of the problems that result from not carefully considering the choice of tests is offered by the Mini-Mental State Examination (MMSE) [138] that has been extremely widely used when considering age-related cognitive decline. An assessment is made under various headings: 1) Orientation – where are we; 2) Memory – repeat the names of three objects; 3) Calculation – count backwards by removing seven from a starting number; 4) Language – repeat a tongue-twister; 5) Perform a three-stage instruction – place paper in the right hand, fold it in half and put it on your knee.

The widespread use of this test has without doubt greatly inhibited the study of the influence of nutrition on the aging process. The test is crude and combines into one score many aspects of cognition that are not similarly related to the aging process. The test was never intended to be used to study short-term responses to nutrition but rather was conceived as an initial everyday means of clinically screening for dementia. In fact the MMSE has been found to correctly distinguish those with dementia on only 65% of occasions and four items have been found to detect the disorder as well as the full test.[139] Although the ultimate criterion is the development of dementia it is arguably not sensible to use this as the dependant variable in intervention studies; unless that is the studies have extremely large samples that have been studied for very long periods. The incidence of dementia at age 65 years is 1% and at 85 years it is still only 25%. As the majority of the population do not suffer with dementia, studies will need extremely large samples to pick up any dietary induced changes in dementia as such, given that the vast majority can be expected not to develop the condition irrespective of the nature of the nutritional intervention. Although those suffering with dementia will tend to perform such tests poorly, the MMSE is unable to measure early signs of cognitive decline, changes associated with normal aging or alternatively subtle improvements. It simply lacks the needed sensitivity and the ability to distinguish those aspects of cognition that decline with age from those that do not. It has been suggested that when examining age-related changes, and there is insufficient time and resources, that a comprehensive test battery should be used. In particular attention should be directed to the assessment of episodic memory as this aspect of cognition is particularly associated with dementia and the early stages of cognitive decline.[56] Episodic memory involves memory for events associated with particular times and places, events that can be verbally described. In contrast semantic memory (the meaning of words, and other conceptually-based knowledge that is not related to an individual's specific experiences) and procedural memory (for example remembering how to ride a bike) do not decline in the same way in those with dementia.

The timing and duration of dietary intervention

Although advancing age is a predictor, an advanced age is not inevitably associated with dementia and there is increasing interest in those who retain their faculties. Nutrition is believed to be an important factor and if we understand the role played by nutrition we may be able to influence the rate that dementia occurs, or the age or speed at which the decline begins. The mechanisms believed to underlie biological aging are potentially susceptible to the nutritional status, including oxidative stress, homocysteine, inflammation and advanced glycation end-points. However, the evidence from intervention trials has been disappointing. For example, a systematic review of micro-nutrient supplementation noted that although observational data suggested a link between micronutrient intake and health outcomes, the evidence from large randomized controlled trials did not support the use of antioxidant micro-nutrients for cardiovascular, cancer, eye health, immune and cognitive end points.[140] Why then has there been a failure to demonstrate a beneficial influence for anti-oxidant supplementation when oxidative stress is thought to damage tissue? One answer is that to date studies have failed to acknowledge the time scale over which diet has an impact. We need to consider both whether there are critical ages when diet is particularly influential and in later life the duration necessary for a dietary intervention to have an influence.

There is increasing interest in cognitive reserve; that is the capacity of the brain to sustain the effects of disease without manifesting clinical symptoms. Some individuals with extensive degeneration of the brain will display few memory problems; others with limited pathology will have extensive problems of memory. Those with larger brains and more neurons are better able to resist the biological changes associated with dementia.[113] It is usual to distinguish the role played by a bigger brain (brain reserve) from how it has been programmed by education and other life experiences. As an illustration of this phenomenon, in the United Kingdom a study of a birth cohort found that cognitive ability at fifteen years of age had greater influence than education on later measures of cognitive decline.[141] Similarly, in a Scottish cohort, a higher incidence of late-onset dementia occurred in those with lower intelligence scores in childhood.[142] This type of finding suggests that one approach to decreasing dementia should be to consider the impact of diet on brain development, to ensure as much surplus capacity as possible. That is we should try to increase 'cognitive reserve'.

The brain grows rapidly during the last trimester of pregnancy and the first two years of life, placing demands on the diet to provide the nutrients necessary for brain development. Inadequate levels of protein, energy, iron and iodine at this critical stage of brain development result in brain damage and a life-long decrease in cognitive ability.[143] Although such clinical deficiencies clearly have permanent consequences, it cannot be assumed that relatively small changes in the diet of those who are relatively well fed will not also have a long-term impact.

There is only one long-term randomized trial in this area, in which premature infants were fed with either a standard cows-milk based formula or one enriched with additional protein and micro-nutrients. This difference in diet, for a median of only four weeks, resulted in advanced social development and motor coordination at 18 months[144] and in boys but not girls higher intelligence test scores at eight years of age.[145] At sixteen years of age intelligence scores were still greater and imaging studies demonstrated that the caudate nucleus was larger in those who had consumed the enriched formula.[146] This study established the principle that even in those who are apparently well fed small changes in diet at a critical stage can have long-term consequences. These findings generate many questions and few answers. It is unclear how critical it was that the infants were premature and hence that the brain was at an early stage of development. We cannot begin to suggest which nutrients, at what doses, were responsible for this long-term change in cognitive functioning and brain structure. The study does, however, establish the principle that the small sub-clinical differences in diet can have long-term consequences. One can speculate that the nature of nutrition, prior to birth, might in this way contributes to 'cognitive reserve' and hence the incidence of dementia late in life.

Having considered neural development, a second consideration is the time scale of any subsequent cognitive decline. One approach to this question is to use imaging techniques to establish the volume of the brain and relate this to the volume of the skull measured using X-rays. The size of the skull is constant whereas the size of the brain declines. Such an approach shows that the shrinkage of the brain occurs progressively beginning at about 20 years of age.[147] Studies of cognitive functioning similarly find that average measures of episodic memory decline with age, scores being the highest in the youngest group tested; those from 35 to 40 years.[57] This evidence of age-related changes in the brain's structure and functioning early in life, contrasts with the time scale over which dementia begins to occur: only 1% of the population will be diagnosed with dementia at 65 years. It seems that the aging process occurs over a long period, such that brain shrinkage begins up to sixty years before dementia is diagnosed. It is reasonable to suggest that any influence of diet may prove to be slow and progressive, such that diet is going to be influential over a much extended period. The question arises as to whether, to date, intervention studies have lasted for a period long enough to protect against the aging process. For example, has the failure of intervention studies to find a beneficial response to anti-oxidant micro-nutrients been simply a reflection of studies that do not last long enough to have a significant influence?

Methodological implications

If this analysis of the time scale of the influence of nutrition is accurate there are considerable methodological implications.[148] The picture is of diet influencing brain development; and then in the adult, having a slow impact over many decades. The desire is always for evidence of causality that comes from randomized controlled double-blind trials. It is, however, difficult to see how dietary intervention trials can last a life time, beginning with the manipulation of the diet of the pregnant woman. Few would question the desirability of intervention studies, but to what extent are they possible in the present context? Individuals cannot be blindly allocated to a dietary pattern that they will follow for a life-time.

Alternative approaches need to be taken. In many instances there may be little alternative to epidemiology, that has been said to allow causality to be assumed when the data satisfy a demanding range of criteria.[149] This does not necessarily cause a problem as questions such as the influence of smoking on health have not been subject to intervention studies, although its adverse influence has been demonstrated using an epidemiological approach.

There is, however, a natural desire to use randomized trials given their obvious advantages, although this inevitably will have to be over a shorter time period: if so it is unlikely that cognitive decline, as such, will be a suitable dependant variable. In most instances changes in cognitive functioning simply do not occur to a sufficient extent over a short time period. An alternative may be to find suitable biomarkers that have been found to have a well established relationship with cognitive decline. The analogy is with heart disease where a demonstration of a decline in blood cholesterol levels is viewed as beneficial. To date firmly established biomarkers in the area of cognitive decline do not exist, although some candidates are discussed above. Alternatively rather than looking for changes in cognition functioning we might use imaging techniques to monitor changes in brain structure, perhaps considering brain shrinkage in areas known to be associated with dementia or alternatively measures of cerebral blood flow.

Nutrition in context

Any attempt to use nutritional means to either stimulate the development of cognitive functioning, or slow its decline, needs to be kept in context. Although diet is viewed in many sections of the population as the cause of problems and the means of solving them, it should be remembered that although diet influences bodily functioning it is by no means the only important factor. Diet needs to be kept in context. Logically all that diet can do is to modify biological functioning: it can increase potential but the exploitation of that potential, with a resulting enhancement of cognitive functioning, also requires a stimulating and supportive psychological and social environment. An interaction between nutrition and a stimulating environment can have long-term consequences.

Although diet influences the incidence of dementia, it occurs less frequently in those who take regular exercise, have mentally stimulating interests, have benefited from extended education, do not smoke, are not over-weight, have a wide circle of friends and social contacts.[150,151] A good diet may potentially reduce the risk of dementia, but in the absence of a range of other factors diet may have little influence.

Similarly there is evidence that a child's development is modified by factors other than diet. The developmental implications of providing psychosocial stimulation (structured play) for malnourished children has been studied.[152] Six months after discharge from hospital those who had

stimulating play were developmentally ahead of a similar malnourished group although both had received remedial nutrition. A combination of both an improved diet and stimulation resulted in development similar to a group of children without a history of malnutrition.

A study in Jamaica followed up children who had been stunted in early childhood. Beginning at 9 to 24 months, for two years they received dietary supplements, stimulation (demonstrations of the use of toys), or both.[153] Perceptual-motor ability benefited from stimulation although supplementation only helped the children of mothers who had better verbal ability. After two years supplementation and stimulation had an additive effect, although this was no longer apparent after four years. The sample was followed up at 11 to 12 years of age although no benefit of supplementation was found in terms of growth or cognitive functioning.[154] In contrast, children who had received stimulation had significantly higher intelligence scores. At 17 to 18 years of age the group was again examined and there was no significant effect of nutritional supplementation, although stunted non-stimulated participants had significantly poorer scores than the non-stunted children.[155] Again a history of stimulation was associated with higher intelligence scores.

It seems as if the effects of dietary supplementation, if provided by itself, might be short lived. Clearly the intention of improving diet is to provide long-term benefits. When implementing such a programme, or alternatively developing a food item with supposed beneficial consequences, the extent to which it is reasonable to expect diet by itself to have an impact should be considered. It is reasonable to suggest that dietary interventions should only be one part of a coordinated approach. After critical early stages in brain development have passed, a change in diet will have a short-term influence on biological potential. Without the opportunity to exploit that potential offered by a stimulating environment, the dietary intervention cannot have long-term impact. A similar conclusion is associated with epidemiological studies and short-term controlled trials. There is a need to monitor and take into account many aspects of the environment, as diet is likely to be influential under some circumstances and not others. The placing of diet into a broader picture will greatly increase the chance of generating significant findings.

CONCLUDING REMARKS

The Symposium on Nutrition and Cognition successfully reviewed the role of nutrition on the cognitive development at early life stage and on cognitive decline in later life. It is recognized that the assessment of cognitive functioning is central to the study of such topics. Although often hoped for, there is unfortunately no standard cognitive test batteries that are suitable for general use. Rather, assessment tools need to be tailored to the target groups and research needs. Advances in technology have looked to bring forth biomarkers capable of monitoring physiological changes in the brain. These tools, coupled with behavioural cognitive assessment may be used to measure the effect of some nutrients on specific cognitive domains. Collaboration and the sharing of expertise between nutritionists, psychologists and cognitive scientists are very important for research in this area.

Following the recommendation from the symposium, ILSI SEA Region will continue to address the assessment of cognitive functioning as a follow-up action. Starting with the assessment of cognitive development for infant and young children, ILSI SEA Region aims to provide a better understanding of brain and cognitive development in early life, and how to assess the role of nutrients in this critical period of development. The report and follow-up activity will hopefully serve as valuable resources for researchers and health professionals to advance both research and the use/dissemination of the findings in this area, particularly in the Southeast Asia region.

ACKNOWLEDGEMENT

The authors thank the speakers of the Symposium on Nutrition and Cognition for providing the materials for report preparation: J Steven Reznick; Saskia Osendarp; Peter Willatts; Namsoo Chang; Lindawati Wibowo; Srinivasan Krishnamachari; Michael Fenech; Andrew Sinclair; Suzana Shahar; Paramjeet Singh; Andrew Scholey; Rachel Galli; Rema Vazhappilly; Jeroen Schmitt; Kathryn Ellis; Richard Head; Toshio Shimizu; Rob Winwood and Josephine Wills. (http://www.ilsi.org/SEA_Region/Pages/NutCogSpeakers.aspx)

AUTHOR DISCLOSURES

There have been no financial or other contractual agreements for this work.

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Special Report

Symposium on nutrition and cognition: towards research and application for different life stages

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營養與認知研討會：關於不同生命期的研究與應用

於 2010 年 10 月在馬來西亞舉辦「營養與認知研討會：關於不同生命期的研究與應用」。回顧飲食與營養對兒童認知發展及生命後期認知衰退的影響。這類主題的研究，其關鍵點在認知功能的評估。認知功能主要包含六個領域：執行功能、記憶、專注力、理解力、知動能力及語言能力，每個領域還可進一步細分。由於人類功能的自然本質，任何認知測驗皆反映數項功能領域的綜合表現；理想的作法，應該用一系列的測試來呈現認知表現的任何差異。在介入性研究中，經常未能顯現飲食改變的有利影響；一個可能原因是研究無法確認飲食效益的時間範圍和關鍵年齡。飲食的影響是緩慢漸進的，使得短期研究很難看到有所改善。此外，因為許多因子會影響人類行為，飲食介入應只是整體對策的一部分；飲食的效應依個人生活的社會與心理情況而有所不同。將飲食放在較廣的社會與心理層面上，會大大提昇產生重要發現的機會。本篇報告就研討會中的簡報與討論做重點描述與回顧。

關鍵字：老化、腦部發展、認知、認知衰退、營養