Nestlé | Research

Nutritional avenues to improved brain health

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Brain health: Why Nestlé is interested

The nutrients and bioactives contained in our food and drink expose our body, including our brain, to a range of potential positive and negative modulators of physiological functioning. It is not surprising therefore that our daily diet and prolonged dietary habits have been associated with acute cognitive and affective states, as well as long-term risks of diminishing performance and neurological diseases. Nutritional effects on brain function are often subtle or not immediately discernible because of their incremental nature.

However, in recent decades, a multitude of mechanistic and functional links have been identified between nutritional factors and brain function. The field of nutrition and brain health holds exciting potential for new discoveries, as well as refinement of existing knowledge. Some of the ongoing development areas at Nestlé Research are outlined below.

At the most basic level, nutrition should meet the brain's demand for energy, essential structural building blocks and precursors and micronutrients to support elementary physiological processes[1]. Inadequate nutritional intake for any of these components will have a negative impact on the brain, as is apparent from the cognitive consequences of major or prolonged malnutrition, particularly in pivotal periods such as during neurodevelopment. Beyond the extremes, suboptimal brain functioning may arise from less overt nutritional deficiencies, particularly in long term. An important extension of this notion relates to defining nutrition necessary to specifically support brain health, as this may differ from those obtained by general recommended daily intakes or include additional nutrient requirements. While being essential to fully exploit the potential of nutrition to support brain health, the construct of brain-specific nutritional requirements is a formidable task. It will require a workable level of granularity, as nutrient levels and types will likely vary as a function of the targeted brain health benefit (e.g., cognitive aging, neurodevelopment, daily performance, affective disturbances) and population characteristics (e.g., age, gender, health state lifestyle, genetics). Advancing insights from human epidemiological and intervention studies that characterize key associations between nutrient levels and brain health will pave the way to establish specific dietary guidelines for specific brain health benefits. Combined with the readily accessible tools to monitor an individual's nutritional status, the concept of personalized nutrition for brain health then becomes attainable.

Combining the potential interactive effects of good nutrition, physical activity and mental stimulation has emerged as a sound approach to facilitate brain health. This has been highlighted by the results of two recent large scale multi-domain intervention studies in cognitive aging: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability[2] and Multidomain Alzheimer Preventive Trial (MAPT)[3]. A similar approach can be employed in the promotion of cognitive development. Further insight on the relative contribution and potential synergies of each of the factors to exert positive brain health effects, as well the interactive effects between each of the lifestyle factors, is needed to refine the most potent and practically applicable programs.

In addition to macro- and micronutrients, food delivers a range of potential bioactive compounds that may exert a wide array of neurobiological effects. The potential brain benefits, for example, of the large assortment of polyphenols found in fruits, vegetables, seeds and derived products such as wine, coffee, tea and chocolate has been extensively investigated[4]. Another example are foodborne probiotic bacteria, which recently emerged as intriguing potential brain health modulators.

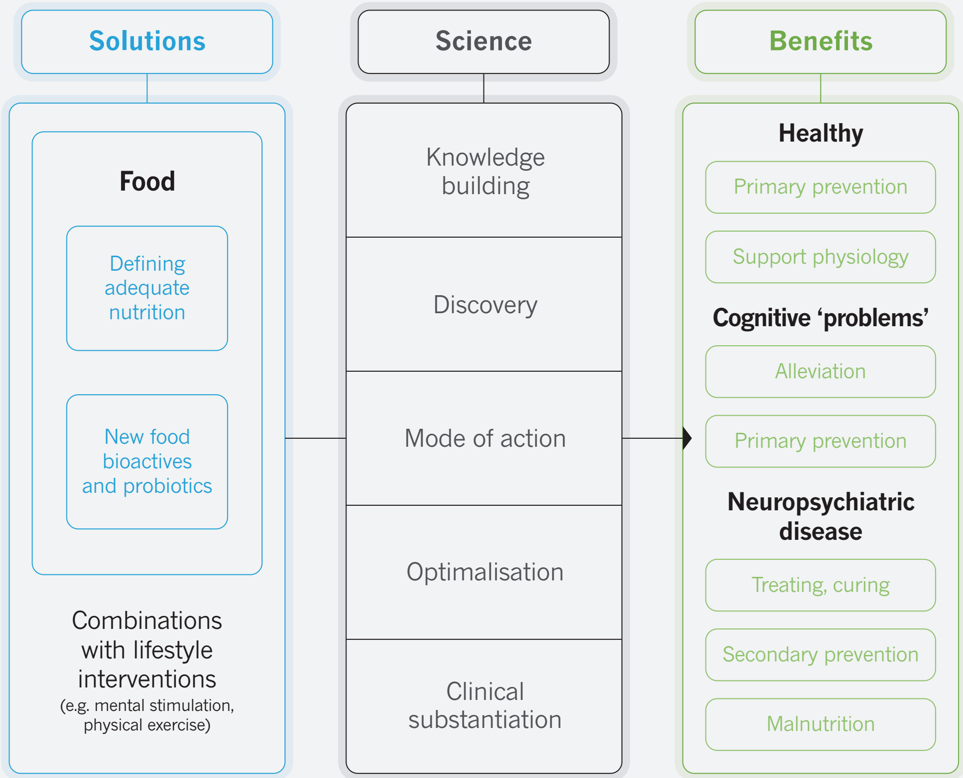

Figure 1 | Schematic representation of the opportunity landscape for nutrition and brain health: interventional approaches, methods and brain health benefits.

The cross-talk between gut microbiota and brain, via endocrine, immunological or neuronal pathways, has been studied for decades, but the notion of targeting the gut microbiota ecosystem to produce brain health benefits has rapidly gained tremendous scientific interest[5]. The emerging scientific insights on the links between the gut microbiome and various neuropsychiatric conditions, particularly related to affective disturbances may provide for nutritional therapeutic solutions based on delivering beneficial probiotic strains, prebiotic compounds, or other nutritional components that may influence gut microbiotic colonization or metabolism (Figure 1).

At the recent 12th Nestlé International Nutrition Symposium on *Cognition and Brain Health* the topic was discussed with the leading and pre-eminent scientists in the field.

Nestlé research on cognitive development in infants and children

One of the most critical developmental stages occurs during fetal and infant life and early childhood. This is when the brain grows most rapidly, and the structural and functional basis for development is being built. Physical, mental and behavioral development not only depend on genetic, biological, and individual factors but also largely on environmental aspects such as nutritional intake and cognitive stimulation[6,7] (Figure 2). Therefore, for Nestlé Research this is a key area of engagement.

Optimal nutrition, particularly during growth and development, is important to reach full physical and cognitive potential. This becomes most apparent when nutrients are insufficient. Developing countries still face a high prevalence of insufficiencies for brain-relevant nutrients, with a correlation between (micronutrient) deficiencies and low socio-economic status[8]. Less consistent findings exist for nutritional intervention effects in otherwise healthy infants and children. This may partially be explained by methodological aspects, but may also be based upon the multifactorial nature of development, which may not be appropriately covered in single-factor interventions.

Cognitive and environmental stimulation of a child are important for cognitive growth and learning. On a neuronal level, experience-based activities stimulate synaptogenesis, myelination and thus brain connectivity[9]. Components of stimulation may include mother-child-interaction, play, learning materials, and systematic education. However, similar to nutrition studies, intervention studies testing the effect of psycho-stimulation alone on cognitive development and socio-emotional outcomes in young children have not been very successful.

In conclusion, the multi-factorial and multi-dimensional nature of child development should be considered in intervention approaches that target cognitive growth. Chances of success regarding effects from intervention trials may increase when multiple domains of a child's encircling factors are targeted simultaneously. Such type of multidomain approaches, particularly combining nutritional interventions with cognitive stimulation, are currently pursued by Nestlé.

Nestlé research on sensory stimulation and cognition

The processes of eating convey to the brain information about food characteristics. Food not only activates brain pathways involved with perception but also with energy sensing and metabolic control. Smelling, chewing or tasting of food induces a variety of physiological responses preparing the body for ingestion and digestion. Nestlé research is focused on the physiology of perception, with emphasis on gustation and chemestesis.

Energy contained in food is crucial for proper brain function, which accounts for about 25% of the calories consumed by our body. Peripheral and central mechanisms underlying the detection of foods with high nutritional value are beginning to be understood. In collaboration with the University of Lausanne (Switzerland), Nestlé scientists established that the visual system provides information about food energy content and that brain regions involved with attention and self-regulation shape decisions on portion size[10]. To investigate the contribution of the human gustatory system in oral energy sensing, Nestlé scientists developed methods to precisely stimulate the tongue with taste while recording brain activity by electro-encephalography (EEG)[11].

In a first step, the chronometry of brain activation after taste stimulation was established with millisecond resolution, from primary to secondary gustatory areas. It turned out that dietary fat, independent of perceived taste and pleasantness, yields sustained activation within the medial orbito-frontal cortex and hippocampus, indicating a reward response. Parallel evidence indicates that sweet tasting sugars and tasteless carbohydrates prompt specific responses within a network encompassing the orbitofrontal area as opposed to non-caloric sweeteners[12]. Altogether these findings suggest the ability of the tongue to probe calorie content distinct from taste signaling. Future studies are desirable to demonstrate the potential of oral energy sensing.

Another area of interest is focused on the impact of food oral processes on arousal and cognitive performance. The ingestion of food engages multiple sensory systems eliciting activation both in the central and peripheral nervous systems. Several studies indicate that sensory stimulations can be associated with enhanced task performance and physiological arousal, for example the chewing of gum and mint flavors. With modern lifestyles, people seek performance enhancement and food products appear as healthy alternatives to other psychoactive compounds used. Combining EEG with measurement of attention performance, a Nestlé study demonstrated the benefits of refreshing perception induced by specific sensory properties (i.e., cooling, tingling and sourness). Relative to a standard water-ice or a glass of water, the consumption of a water-ice optimized for refreshing perception enhances EEG oscillatory activity in the alpha range in favor of improved performance of attention. The impact of food flavors on cognitive function is seen *in utero* and during the first months of life. Flavors from foods eaten by a mother can enter the placenta altering the composition of breast milk to induce learning, which in turn will impact behavior and health throughout life.

Figure 2 | Cognitive and environmental stimulation of a child are important, as is correct nutritional intake.

Certain sensations linked to spices are related in their physiology more to the pathways of pain and analgesia than to taste. Only with the discovery of the transient receptor potential (TRP) channels the molecular basis of this phenomenon became available. When it comes to aging, spices not only compensate for taste loss but they also help in the management of altered eating processes such as deglutition. The difficulty of swallowing, or dysphagia, is a common complaint among older adults and patients with neurogenic disorders. A swallowing reflex can be stimulated by electric or magnetic currents applied to specific brain regions or to the pharyngeal region. Brain activations elicited by food flavors overlap with regions involved in the control of swallowing. The Clavé laboratory has shown that activation of the trigeminal pathway by capsaicinoid compounds improves the safety, efficacy and physiology of the swallow response in dysphagic patients[13]. Nestlé Research is currently engaged in this domain – combining molecular, sensory and clinical approaches – to develop natural food solutions for patients with dysphagia.

Nestlé's interest in research on epilepsy and depression

It has been recognized for many centuries that prolonged fasting leads to a marked reduction in the number of seizures experienced by people with epilepsy. It was not until the early 1920s, however, that researchers discovered that fasting leads to ketosis (i.e., the elevation of ketone bodies in the body as an alternative source of energy), and that a diet rich in fats and low in carbohydrates can induce ketosis and thus mimic prolonged starvation. Soon thereafter, the 'classic' ketogenic diet was established and became popular as a treatment for epilepsy[14], long before the first anti-epileptic drug, phenytoin, became available in the late 1930s. Subsequently, the ketogenic diet concept was improved in the 1960s by using medium-chain instead of long-chain triglyceride-based diets which allowed for a slightly better choice of foods.

Randomized clinical trials have shown that the efficacy of the classic and MCT (medium-chain triglyceride) ketogenic diet for seizure control in children is approximately equal to that of available anti-epileptic drugs[15].

A main limitation, however, of the ketogenic diet is its poor tolerability. Because at least 75% of daily calorie intake must stem from fats for it to be efficacious, food choices are limited. This dietary restriction is only tolerated by a small proportion of patients so is more appropriate for children with treatment-resistant epilepsy, in whom diet can be better managed and supervised.

In contrast to its well-established efficacy, the mechanistic basis of the ketogenic diet for seizure reduction is not well understood. While a diverse number of anti-seizure potential mechanisms have been proposed, it is unclear which may be driving efficacy and to what degree the observed effect is multifactorial. More recently, direct anti-seizure effects of the free fatty acids that form the medium-chain triglycerides have also been suggested, such as inhibition of glutamatergic neurotransmission and improvement of mitochondrial function. These are promising fields of research

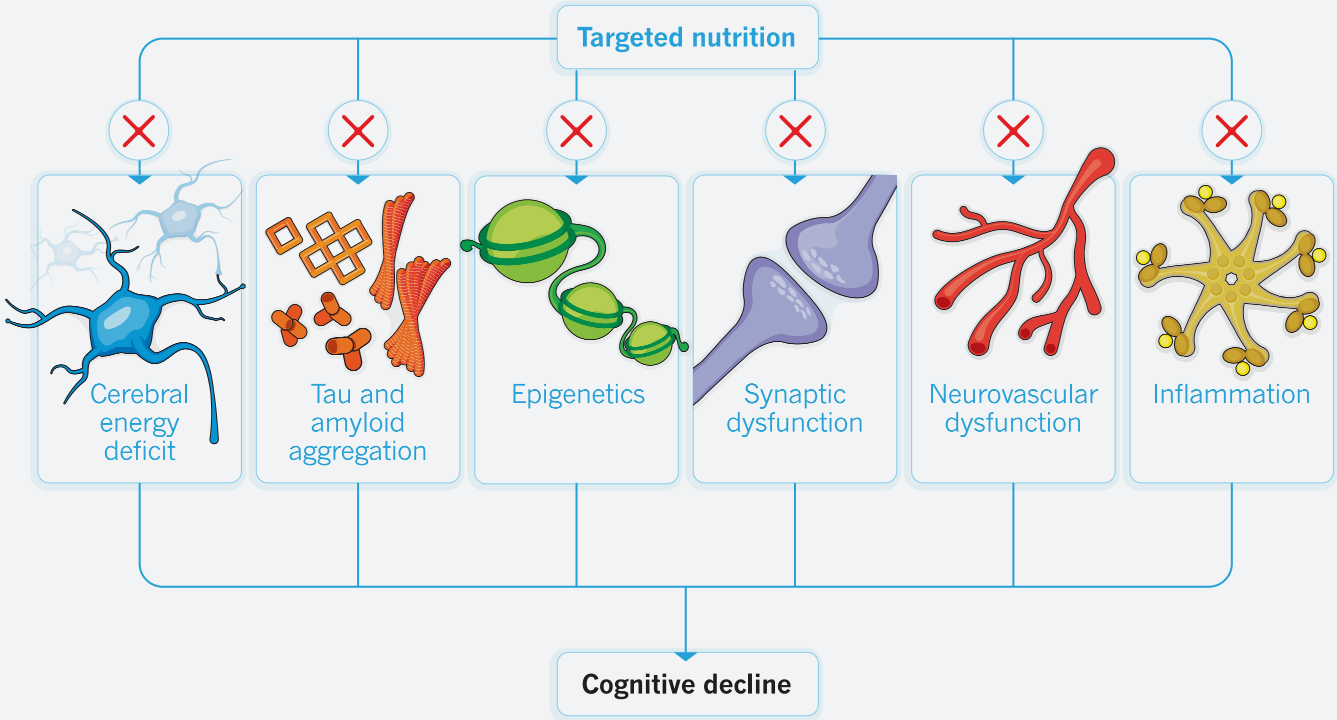

Figure 3 | Targeted nutrition for age-related cognitive decline and Alzheimer's disease.

which we hope will result in an improved mechanistic understanding to inform the next generation of epilepsy treatment options.

Major Depressive Disorder (MDD) is a common and heterogeneous psychiatric disorder that imposes a high burden of suffering on patients and has a high cost to society. Although heritability studies have shown a significant causal contribution to the disease, very few (if any) single gene signals have been consistently linked to MDD. There are thus few rational starting points to develop new therapeutic approaches founded on an understanding of causal disease biology, and the mainstay of available treatments will continue to be based on the reuptake inhibition of serotonin and norepinephrine, two mechanisms identified by serendipity[16].

An alternative approach aims to identify peripheral biomarkers of how plasma levels differ between patients with lifetime MDD and healthy controls. Among many studies conducted in this field, some papers have described lowered levels of B vitamins and elevated homocysteine levels in MDD, thus implicating the one-carbon cycle as a possibly relevant mechanism. It needs to be emphasized, however, that these studies are observational and cannot definitively rule in or out causation with a case-control design.

Nevertheless, a placebo-controlled, randomized clinical trial has recently reported a beneficial effect of L-methylfolate (a naturally-occurring derivative of folic acid or vitamin B9) at the higher dose of 15 mg/d in treatment-resistant depression[16]. It will be important to conduct additional studies to better understand a possible dose-response relationship between L-methylfolate and antidepressant response.

A platform at Nestlé for individualized nutritional therapy in aging and Alzheimer's disease

Alzheimer's disease (AD) is a serious global public health problem. Strategies for prevention are a high priority, and innovative nutritional strategies represent a plausible but under-utilized approach. The standards of care for prevention and treatment of AD are glaringly lacking in the areas of nutritional assessment and intervention. While assessment of vitamin B12 status is routinely recommended, assessment of other nutritional risk factors is not mentioned in existing practice parameters. Treatment of putative risk factors is not recommended in the absence of clinical trials documenting efficacy of such interventions. Clinical trials of nutritional intervention have typically followed the model of drug studies, applying the maximal tolerated dose to a population of all subjects with a diagnosis of AD or at risk for dementia, rather than limiting participation to subjects at "nutritional risk" with evidence of nutrient depletion.

Nestlé strives to develop new technologies and approaches that address multiple nutritional parameters and better tailor the nutrition to the individual. Applying this concept in randomized trials is challenging, and requires the development of more "holistic" methods for the assessment of patients. This approach is particularly attractive in light of some failed nutritional interventions, such as high-dose vitamin E for subjects at risk of AD[17], homocysteine lowering strategies for dementia prevention[18], and omega 3 fatty acids for slowing AD progression[19]. In each case, a more holistic multi-factorial assessment of nutrient status, genetics, and treatment may have permitted a more effective study design or data analysis. However, it is simply not feasible to evaluate patients' nutrient status in its entirety. Here we provide a brief overview of the risk factors for cognitive decline and AD and highlight some key biological areas to approach with nutrition.

The neurobiology of Alzheimer's disease is complex and multifactorial (Figure 3). About 58% of late onset AD risk is heritable and the most relevant genetic risk loci have been identified, providing valuable insights into the underlying mechanisms of the disease. The gradual loss of parietal and temporal functions results in impaired memory, agnosias, apraxia and language symptoms that eventually disrupt daily activities. These are preceded by several years of underlying pathological changes in the brain, including early disturbances in amyloid, tau and brain energy metabolism. The structural changes (i.e., synapse loss) that result influence cognitive function. In this context, new stages for intervention are being described and proposed. Understanding of the natural history of age-related cognitive decline and AD will continue to evolve in the future as new technological advances emerge, particularly in the area of biomarkers. Currently, the most well established risk factors for AD include: age, inheritance of the apolipoprotein epsilon 4 allele (APOE4), low cognitive and physical engagement and head injury. Vascular risk factors, including hypertension, diabetes, depression, alcohol consumption, mid-life obesity and hypercholesterolemia also increase risk for AD. Dietary risk factors include lower intakes of folate and other B vitamins, vitamin E, fish and other unsaturated fatty acids, vegetables, berries and carotenoids, and more recently flavonoids, vitamin D, and distinct dietary and nutrient biomarker patterns have been implicated[20]. The subsequent randomized trial testing of a single or few nutrients supplemented at high dose for the prevention of cognitive decline have been mostly disappointing. However, the trials that targeted subjects with sub-optimum nutrient status at baseline appeared to benefit from supplementation, highlighting a key element of trial design that has been underappreciated thus far. Another aspect of the subject enrichment strategy, other than poor nutritional status at baseline, is to consider the presence of disturbed neurobiology that is the hypothesized target for the nutritional intervention. For example, if the nutritional therapy has shown anti-amyloid effects, then enrolling people that are depleted of that nutrient under study and with evidence of amyloid neuropathology may be the best strategy. One prevention trial is enrolling only older adults at risk of dementia with low omega-3 fatty acid status and higher MRI derived white matter hyperintensities at baseline to prevent cognitive decline (ClinicalTrials.gov Identifier: NCT01953705). Another example is the Axona trial testing a medium-chain fatty acid to remedy cerebral energy deficit in mild to moderate AD that targets APOE4 negative subjects who appear in preliminary studies to appreciate such a therapy. The multi-domain FINGER and MAPT trials alluded to earlier, highlight a comprehensive intervention with components of nutrition, cognitive and physical engagement. These trials are good examples of targeted and multi-domain interventions that hold much promise in the future. Nestlé is committed to building the scientific foundation for how nutrition influences brain health and translating that knowledge into nutritional approaches that help address the public health and economic burdens that accompany cognitive decline and Alzheimer's disease.

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