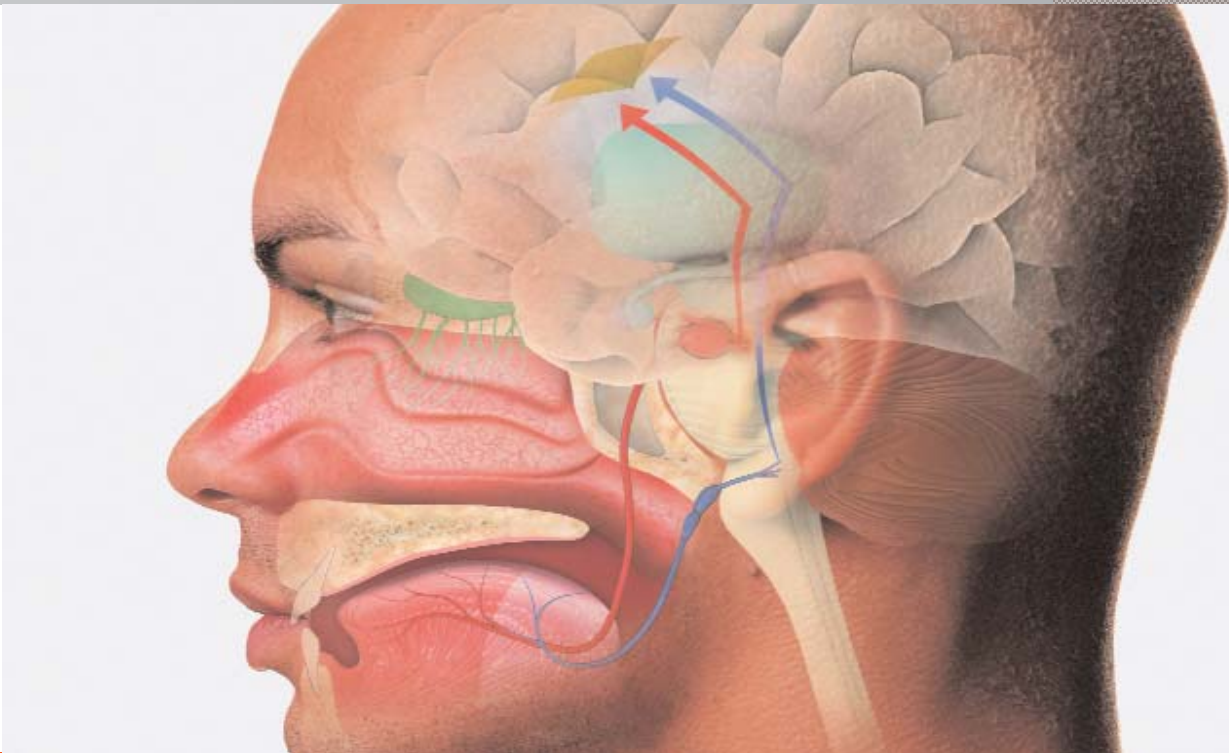


Food and Nutrition Communication

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Nutrition and the Brain

The brain is one of the most complex organs in the body and despite being the subject of a great deal of research, is still the one we know the least about.

The brain contains about a hundred billion neurons surrounded by glial cells whose main role is to provide them with energy. Neurons communicate with each other by electrochemical signals. Every neuron receives signals from myriads of other neurons and the messages are grouped in structures with specific functions.

Although the connections between our neurons are constantly and rapidly changing and being re-wired, we are all losing brain cells every day as we age.

In this edition, we take a look at whether nutrition can influence brain development and performance, and whether there is anything we can do to limit functional decline.



Our brains are determined primarily by genetics. However, favourable environmental factors also play an important role.

Evolutionary Background

Plants, animals and human beings originated from one single cell – LUCA, or *Last Universal Common Ancestor* around 3 billion years ago. LUCA did not arrive as a ‘big bang’ but was itself preceded by millions of years of molecular evolution. From this moment on, most of the constituent information for subsequent forms of life was present in the cell.

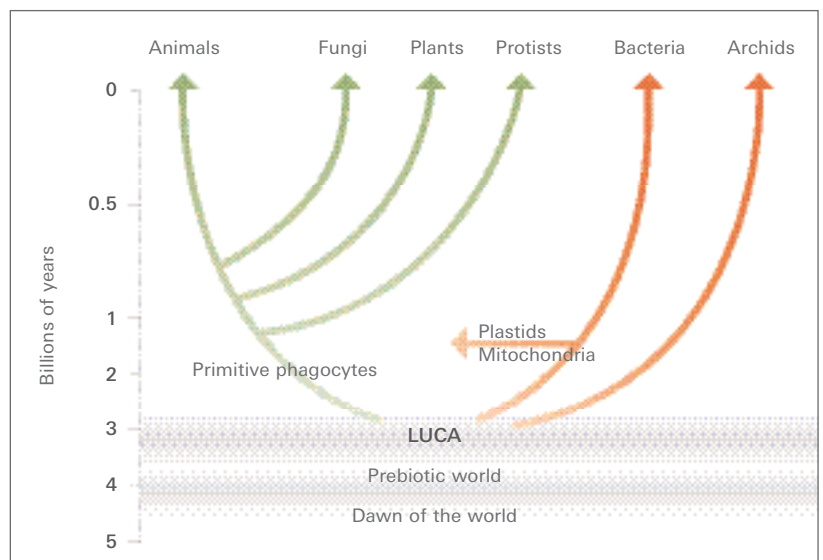
Evolution depends on two factors: **stability** – to maintain one generation to the next, and **variability** – without which there would be no adaptation. Variability allows the best matches between the species and its environment to be selected [1].

Animal life originated in the sea, and continued to evolve for hundreds of millions of years during which new species continued to emerge. In the transition from water to land the nutritional environment changed dramatically. Another major development was the emergence of mammals, and unlike the amphibians and reptiles, which laid eggs in a hostile environment, mammals kept their young in much more favourable conditions inside the body, fed through the placenta. Under this more favourable environment, mammalian species gradually developed larger brains. Today we know that **70% of the calories from the placenta are devoted to brain growth of the foetus**. Human beings have lived for millions of years, but major brain changes are thought to have occurred in the last 200,000 years.

What could have caused the change in human brains to become the sophisticated computing systems they are now? Could this have something to do with what human beings began to eat, its abundance or its scarcity?

Of course, genetic potential is the overriding factor. However, some nutrition researchers claim that better nutrition enabled certain communities to obtain the maximum of their genetic potential, and maintain it over a sustained length of time thus creating better genetic selection.

It is an understatement to say that not all scientists agree on this idea, but two major claims in paleo-nutrition were that human colonies living near the sea experienced major brain improvements. In parallel, DHA (docosahexaenoic acid) was a large contributor to brain growth and that DHA was found in seafood. Other colonies living inland such as the Australopithecines retained small brains for the next 3 million years. There are some who propose the idea that DHA had a direct effect on brain development, but conclusive evidence is missing. A very large number of other factors could also account for this evolution. Perhaps the reasons for the smaller brain of the Australopithecines included a food supply that was less reliable and of less useful quality. Neanderthal man ate mostly red meat from animals that roamed Europe at the time. But human remains found in Britain, Russia and the Czech Republic dated 20–28,000 years ago showed that



Source: Luc Ferry, Jean-Didier Vincent: *Qu'est-ce que l'homme?* Odile Jacob 2001



fish and seafood accounted for 10–50% of their dietary protein [2]. There is much interesting speculation. But we shall see further on which elements are just as important for brain function – for example, iodine.

What is in a Brain? Answer: mostly Fat! (About 60% of the brain is composed of lipids).

The membranes of neurons are composed of a thin double layer made mainly from fatty acid molecules. Glucose, oxygen and micronutrients pass through the cell membrane to nourish the brain cells and provide the fuel necessary to conduct nervous impulses. Myelin, the protective sheath that surrounds neurons, is composed of 30% protein and 70% lipid. The brain needs lipid for insulation, and for the speed of operation of neuronal messaging.

What fuel does the Brain run on? Answer: almost entirely on Glucose.

Brain Energy Basics

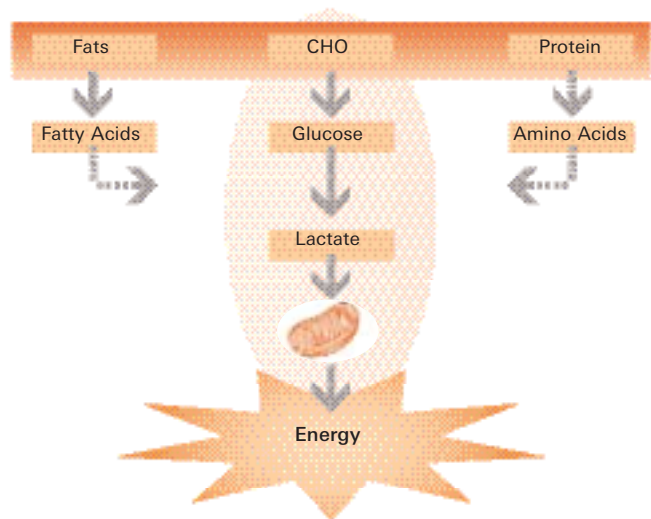
Brain energy supply

Blood glucose levels ensure adequate supply of glucose to the brain, but in very active brain regions, local shortages may occur in the case of high-effort, complex, or prolonged functioning, and when blood glucose levels are relatively low.

Glucose intake improves cognition in adults. The effect is rapid but of short duration (15–60 minutes). The effect has been tested against a zero calorie control, and also in the morning after an overnight fast.

Adequate hydration is essential to both physical and mental performance, (see also *Food and Nutrition Communication, January 2006 – Good Food for Healthy Ageing*).

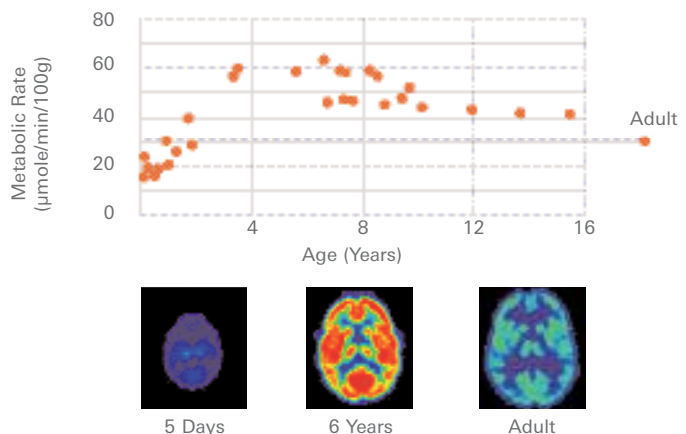
Brain energy—the basics



The brain is highly active metabolically. Under normal conditions its principal fuel is glucose. The brain can use amino acids as fuel but the extent is very limited. The brain cannot use fatty acids directly as fuel. However it can use ketone bodies, which are derived from fatty acids, particularly during periods of starvation.

Ketone bodies are particularly important as a fuel for brain and other nerve cells during starvation. In this state, once glycogen reserves are exhausted, the rate at which ketone bodies are produced from fatty acids by the liver is increased. This makes them increasingly available for use as a metabolic fuel for several organs of the body, but especially the brain. The reason why the brain switches from glucose to ketone bodies as its major metabolic fuel during starvation is to reduce its demand for glucose. If this did not occur then glucose would have to be synthesised in relatively large amount from muscle protein (by gluconeogenesis), which in turn would lead to increased muscle wasting. This 'glucose sparing' effect of the ketone bodies is an important adaptation to the stress of starvation.

The child's brain needs even more energy



Chugani, H.T., *Neurodevelopmental Neuroimaging*, New York 1996.



The brain's preferred metabolic fuel is glucose, but many other substances are necessary for correct functioning. An expert committee has formally approved nutrition claims for the list below, but ongoing research in this field is showing promising results for other substances, such as choline, for example.

Thiamine and Niacin (B group vitamins) are necessary for neurological function.

Folate is necessary for the normal structure of the neural tube in developing embryos.

Cyanocobalamin (Vitamin B12) is necessary for the normal structure and function of the neurological system.

Vitamin C is necessary for normal neurological function

Iron is necessary for normal neurological development in embryos.

Copper and Iodine are necessary for normal neurological function.

Source: UK Joint Health Claims Initiative to the Food Standards Agency, 17th Dec 2003

The brain is like a muscle

When brain is active...

- ↑ Glucose utilisation
- ↑ Oxygen utilisation
- ↑ Blood supply
- ↑ Heartrate
- ↑ Bloodpressure



Some mineral functions, deficiencies and potential toxicities

Magnesium deficiency can cause restlessness, nervousness, muscular twitching and unsteadiness. Acute deficiency can progress to apathy, delirium, convulsions, coma and death. However contrary to popular belief, magnesium deficiency is rare.

Manganese is a trace mineral involved in carbohydrate metabolism and brain function. Miners of manganese in South America have developed manganese toxicity called "Manganese Madness", with neurological symptoms similar to Parkinson's disease.

Copper is involved in iron metabolism and brain function. Deficiency causes anaemia with inadequate oxygen delivery to the organs. Copper deficiency also impairs immune system response and changes in certain chemical receptors in the brain and lowered levels of neurotransmitters.

Zinc protects against cell and membrane damage. Deficiency can cause neurological impairment and influence appetite, taste, smell and vision. There is no upper limit on zinc naturally occurring in food.

Selenium is involved in the synthesis of certain hormones and for cell protection. Deficiency is very rare, but toxicity has occurred in regions such as China, where soil content of selenium is very high. Toxicity causes nervous system damage.



Brain damage due to alcohol

How alcohol affects the brain depends on dose. Very low doses can have the positive effect of reducing damage caused by mental or emotional stress and can actually improve response times. However higher doses bring a formidable range of damaging consequences. Apart from gradually destroying the liver, chronic alcoholism is related to brain damage. In sustained high doses **alcohol shrinks the brain**.

There has been discussion relating to whether women's brains are more vulnerable than those of men to alcohol toxicity. A clinical trial held in Germany [3] to test this hypothesis found a similar degree of brain shrinkage between men and women, but with damage occurring after significantly shorter exposure to ethanol in women. The study therefore corroborated the view that women have enhanced vulnerability to acute and chronic complications of alcoholism compared to men. The pharmacokinetics of ethanol are different in women and men because most men have a form of ethanol dehydrogenase in their stomachs whereas most women do not. As a result men start breaking down ethanol faster than women, less gets in to their blood, and what does is cleared more quickly.

Foetal alcohol exposure has multiple bad effects on infant brain development and represents a leading cause of mental retardation.

CT scans reveal significant alterations in brain **topography** of alcoholic people, particularly in the ventricular system and the inter-hemispheric fissures. Greater **cognitive impairment** is seen in people suffering from alcohol dependence compared to subjects matched for age and education.

Brain development in Babies

Brain volume doubles between birth and six months of age, triples from birth to two and will reach adult volume at around five years of age. The brain remodels its prototype at birth as unused neurons disappear and more frequently stimulated ones increase their number and connections resulting in a complex network. This illustrates the importance of stimuli during the critical period of the early years. Direct psycho-social stimulation of the child through contact with its mother (and father) is one of the most significant elements in brain development in early childhood. At the foetal stage, the brain is quite well protected against most mild nutritional deficiencies. Iodine deficiency, however, causes mental retardation, and a shortage of folic acid in the early stages of pregnancy can be responsible for neural tube defects.

New-born babies smile and gurgle in response to sweet tastes such as breast milk, and screw up their faces at bitter tastes, expressing instinctive aversion to tastes likely to indicate the presence of toxins. This preference seems to persist throughout life even when "safe" bitter tastes have been learned and assimilated, for example the taste for vegetables. Sweetness and fat stimulate the release of endorphins, which are endogenous opioids. Many believe this innate preference for sugar and fat is a better explanation for chocolate "cravings" than a specific plant substance in cocoa.

Iron deficiency in infants

This is the most prevalent nutritional deficiency in both developed and developing countries. It has been estimated that iron deficiency anaemia affects more than **25%** of infants worldwide. Moreover, it is clearly demonstrated that iron deficiency anaemia is associated with psychomotor and cognitive development impairments. Infants suffering from iron deficiency anaemia have lower mental and motor development scores. Iron sulphate supplementation improves



both mental and motor performance *in established cases* of retardation. This does not mean “the more iron the better” for all babies, however, and no significant improvements to normal brain development should be expected from increasing iron through supplementation. On the contrary, each child needs to have the correct amount, no less and no more.

Breast milk contains just what babies need because they were born with iron stores. Iron-fortified infant formula contains more iron, because iron from breast milk is absorbed at up to 70% whereas iron from formula is absorbed only at an average of 11%. The Committee on Nutrition of the American Academy of Paediatrics recommends that “*infants who are not breastfed or are partially breastfed should receive iron-fortified formula from birth to 12 months*”. Infants’ iron needs change during their first year.

Iodine deficiency in infants

When iodine is scarce in food, which is the case in some mountainous areas and areas far inland, not only the transplacental transfer of iodine from the mother to the foetus can be insufficient, but also breast milk will have a subnormal iodine content. Iodine deficiency produces mental retardation. In inland areas such as Switzerland, iodine is added to table salt as a public health measure to prevent this problem at the population level.

Iron overload in adults

In the elderly there is indeed a strong correlation between increased iron levels in some parts of the brain and Parkinson’s disease. Although the reason for this accumulation is still unknown, it may cause oxidative stress that damages brain lipids and dopaminergic neurons. Iron is not the only culprit; other factors play a role in the complex mechanism of this disease. Population-based, case-control studies have reached contradictory conclusions on the effect of iron intake in adults and Parkinson’s disease. Parkinson’s disease affects around 1% of the population worldwide [8, 9].

The Nestlé International Nutrition Symposium – Nutrition and the Brain

The 3rd Nestlé Symposium, held in October 2006 invited world experts in neurological research and nutrition, to discuss the science of the brain, and to focus on its role in influencing how we sense and respond to food. Among the most important research areas in the regulation of human metabolism, are the ways in which body metabolism is controlled by the brain. Both the regulation of metabolism and the basis of dietary choice lie in the brain. An aim of the Symposium therefore was to examine the role of diet in brain functions, particularly:

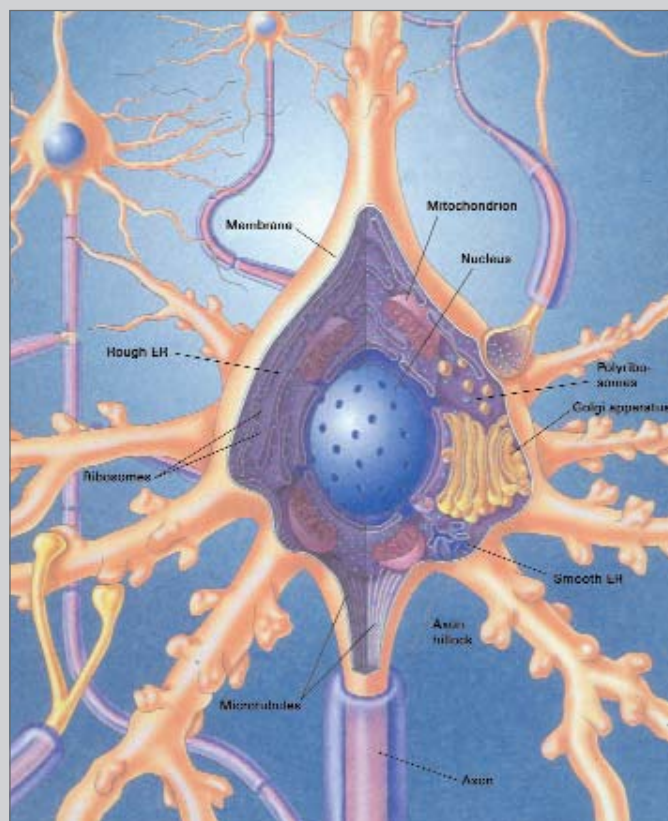
- *how the brain acquires information,*
- *the structure of the brain and how it processes information*
- *how the central processing units of the brain obtain their energy*
- *the signals that the centre core of the brain uses to control itself*
- *problems that develop as the brain begins to deteriorate.*

The following short summary is based on a presentation of the symposium given by Prof. B. German of the NRC. (*Scientists at any Nestlé facility with access to the NRC intranet can view the complete presentations on this site*)

The tongue – how do chemicals on the tongue produce signals in the brain?

We now know much more about how the sense of taste works. In fact this research has found that some of the previous ideas about how the process worked were quite wrong. We were taught as children that the tongue was mapped out into four sections each tasting sweet, salty, acid and bitter tastes. Now we not only know that there is there a 5th taste, umami, but also, (and this is new) that the tongue detects all these tastes all over its surface.

Sweet taste, the sensation provided by simple sugars is not sensed by a single protein, but by pairs of proteins acting together to form a chemical receptor. Interestingly, we have an almost identical sense system for amino acids. Thus our brain is informed of the presence on our tongue of sugars and amino acids and the message in the brain is "swallow - this is good". In parallel to these two kinds of receptors signalling something good, there is a family of very similar protein



Source: Johns Hopkins Mind-Brain Institute

receptors that bind to molecules that resemble plant toxins. These receptors are wired directly through cells and neurons to the brain and the brain interprets these signals as "bad". These are the bitter receptors. We have a large number of slightly different receptors on the tongue in order to sense many different kinds of toxic molecules. What is quite surprising is that we do not consciously discriminate between these tastes. They are all just "bitter". The brain issues a warning about these foods i.e. "this is toxic - do not swallow this, spit it out".

Intestinal taste receptors

How does the intestine affect food preference? Recent studies have shown that intestinal tissue also contains taste receptors. Even though these receptors are not connected to the same regions of the brain, the brain uses this information to make decisions about the food being digested [5].



Appetite and food intake control

In ideal circumstances there are a large number of sensing mechanisms from the gastrointestinal tract to the brain to control the intake of food. However, these messages can be 'ignored' (in some people and under some conditions) by conscious or subconscious decisions based on environmental or emotional considerations.

An area of the brain, the nucleus accumbens, is the centre of pleasure and reward systems. Addictive behaviours involving the intake of neurologically active substances (e.g. drugs) also stem from cues from this small area. The brain is thought to have a so-called "homeostatic regulator" which should, theoretically at least, prevent conditions such as obesity. However this regulator can, in certain conditions, be overwhelmed by the cognitive and pleasure-seeking brain, whose receptors in the nucleus accumbens encourage us to pursue indulgent behaviours and the "thrill of living on the edge".

It has also been pointed out, when discussing obesity, that negative feedback from the systems shown in the schema above, might arrive in the brain too late to have an effect on meal intake. Apart perhaps from the "stretch" receptors in the stomach, most of the receptors start acting once the food is already ingested, and people today tend to eat high calorie foods at high speed. Amnesic patients can easily eat two meals, one straight after the other if they have forgotten they have already eaten. The homeostatic regulator, which is strong on preventing hunger, but weak on preventing over-consumption, presumably provided an evolutionary advantage, to ensure that animals maintained energy reserves, (for example for hibernating mammals).

How does the brain process information?

The brain establishes an astoundingly complex "canopy" of interconnected neurons and constantly restructures these connections in response to the ongoing signalling between neurons. The electrical signals that move information from one neuron to the next are tremendously demanding of energy. As a result the brain is in many respects the most energy-demanding organ in the body. It is now possible to calculate the precise fuel demand. The energy needed to transmit signals from neuron to neuron limits the brain's capacity, so the need to keep it well fuelled is essential. All of the requirements for fuel for the brain must be satisfied by the diet.

Brain imaging

Thanks to the new technologies of brain imaging, it is now possible to capture images of the brain as it functions. Scientists have even found ways to image specific molecules in the brain. Our senses of taste, smell, touch, vision and hearing, when activated by food cues, can 'light up' entire regions of the brain with activity. Mental performance is the measurable output of all of the brain functions acting in coordination. The mechanisms by which mental performance develops and the key determinants of this astonishing output are not fully understood. Recently, however, the technique of brain imaging is allowing scientists to begin to make real-time observations of the brain as our bodies perform certain functions, and their effects on the brain itself. While many human activities involving the brain are being studied, one thing is certain: eating causes a dramatic increase in activities throughout much of the brain.

Computing the brain's key unit

Many of the key properties of single neuronal cells are now known with a high degree of mathematical accuracy. In a very ambitious project, researchers at the EPFL proposed to IBM to take these complex mathematical functions for individual cells and combine them to construct a model of the human neocortical columns (approximately 10,000 neurons) using their IBM supercomputers. The Blue Brain project is now a reality and this combination of biological and mathematical formulation, brought together as one of the world's largest computer projects, is beginning to show how brains function and develop, and also what could cause failures in those processes, such as autism, schizophrenia and Alzheimer's disease.

Connections between neurons can be compared to connections between friends and acquaintances. Neurons tend to neglect old connections when confronted with the need to rapidly form new connections to cope with new environments. The constant re-wiring and re-configuration is limited by energy supply however, and the brain connections gradually fall back on a smaller circle of connected neurons like a number of "good friends" shown to provide reliable information. The result is that micro-circuitry of neurons is constantly being expanded, contracted and re-configured with experience. The reconfiguration can take just a few hours. Failures to execute these complex connections correctly are responsible for certain neurological diseases.



Autism is thought to occur when there is an abnormally expanded circle of connected neurons and the neural micro-circuits become autonomously active, and lack a limiting and centralizing factor, and therefore cause the subjects to withdraw into themselves.

Jet-fuel for the brain

As the brain developed through evolution, it developed a solution to cope with the huge need for fuel. It disassociated neuronal activity from the fuelling activity by introducing a special type of cell – the Glial cell. Glial cells take in glucose from the blood and convert it to an assimilable form which is lactate. Glial cells are the turbo chargers pumping lactate to fuel the neurons. Very recent results indicate that Glial cells might also be implicated in the coordinated processing of information and action potentials across whole regions of the brain.

Food for Thought

Whenever signals are being processed in the brain very large amounts of energy are being consumed. Nature uses parallel processing and plasticity in the connections to achieve a signal processing power which is still superior to that of present day computers. Nonetheless, the brain is limited by its ability to fuel its signalling. Furthermore, synaptic vesicles must be re-cycled to form new synapses and innumerable dendritic spines during various forms of synaptic plasticity, and this recycling of proteins also uses massive amounts of energy. Therefore it should not be surprising that the brain involves itself in regulating all of the body's metabolic and energetic processes. The most recent scientific research finds that the brain has a controlling influence not only in allocating energy from adipose to muscle, heart, liver etc., but also in deciding what to eat and when, and when to stop. Should it really be a surprise that the brain finds such pleasure when we ingest its favourite food – sugar?

Central command

The brain takes up signals of energy status from all over the body and **integrates** this information to maintain a balance.

When the brain fails to integrate the signals correctly – or some overriding instruction from the psyche or cognitive brain intervenes – the result can be obesity, or at the other end of the scale: anorexia.

Alzheimer's disease and a role of insulin

The Symposium ended with a general discussion on Alzheimer's disease and present day research into prevention and treatment.

Insulin has converging effects on inflammation, memory, and the regulation of beta-amyloid – the peptide that plays a key role in the pathophysiology of Alzheimer's disease.

There are insulin receptors throughout the brain, localized at the synapses. Insulin readily crosses the blood brain barrier where it binds to receptors in the hippocampus. Insulin at optimal concentrations actually enhances memory, presumably by promoting the uptake of glucose to fuel the brain and the connections needed to establish memories. Insulin is secreted and cleared within 8–12 minutes in ideal circumstances. However, chronic insulin secretion from continuous eating and poor diet can lead to insulin resistance. Insulin resistance means that cells that should respond to insulin by taking glucose from the blood fail to do so. This results in the paradoxical situation in which cells are starved for fuel in a pool of excess glucose. Observational studies have found that individuals with insulin resistance and its accompanying peripheral hyperinsulinemia are at increased risk for memory impairment and various forms of dementia in later life.

Chronic high levels of circulating insulin are also associated with levels of inflammation and neurotoxic peptides in the central nervous system. Adults with insulin resistance also show a reduction in cerebral glucose metabolism in brain areas that also characterize early Alzheimer's disease. There are other, notably vascular conditions involved in the development of Alzheimer's disease, but insulin resistance is now shown to be a key co-factor.

(More on Alzheimer's disease and nutritional approaches to treatment further on.)



The Sense of Taste

The sense of taste is a very sophisticated process of chemical signalling. All animals including humans regulate their intake of the necessary food through five basic taste “modalities” sweet, bitter, sour, salty and umami (a meaty taste). In essence; ***the sweet taste signals the identification of energy rich foods, umami recognizes the amino acids of proteins, salt ensures the proper electrolyte balance and sour and bitter tastes warn against potentially toxic or poisonous intakes.*** It is through taste perception that in normal circumstances the body regulates its proportional intake of nutrients. The taste system, made up of taste receptor cells clustered in taste buds at the surface of the tongue and the palate, plays a key role in whether we decide to swallow or reject food.

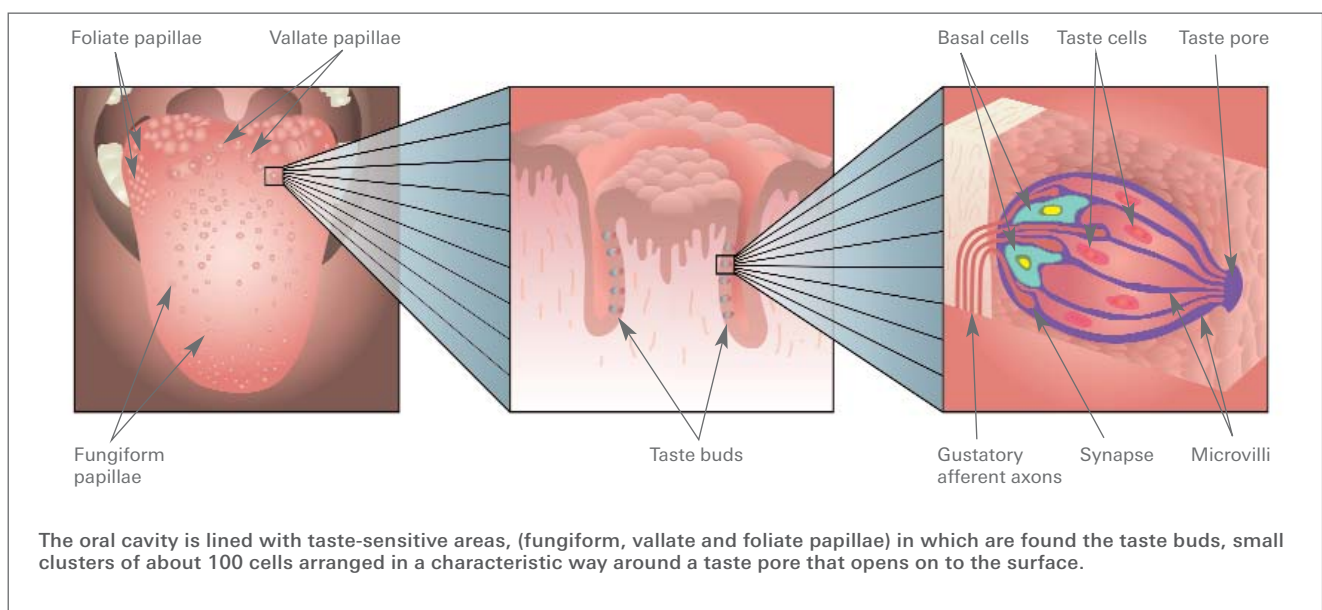
Research into taste requires isolating the genes which signal taste. It also requires tracing the pathways from the tongue and surrounding areas to the brain, which in turn activates various other circuits affecting behaviour.

By sensing the five taste modalities, (sweet, sour, bitter, salty and umami), our sensory apparatus acts like an analytical chemical laboratory making independent measurements of ionic equilibrium, toxicity and nutritional value. Subsequently, the processing and ‘filing’ of this information in specific areas of the brain leads to the development of a perceived taste profile. These perceptions lead eventually to a pleasure-driven classification of likes and dislikes, needs and avoidances.

Once again, taste is rather a primitive aspect of our ability to identify specific foods. We actually use olfactory and visual cues more than taste per se.

Two systems modulating food intake and food uptake

Taste stimulation from the mouth is projected into defined cortical areas in the brain, resulting in taste perception. Similar information from receptors in the digestive tract initiates a metabolic response to the food present there. There seems to be no direct communication with the sensory areas of the brain, so interestingly the



signalling appears to pass via the autonomic nervous system.

A picture is emerging in which different detailed and primarily independent "measurements" of ingested food are being made by similar receptor systems, one in the mouth and the other in the gastrointestinal tract. Thus, while the sensory-linked receptor system in the mouth is the gatekeeper for food intake into the digestive system, the intestinal receptor system appears to be involved with absorption of food into the body [4].

How taste information reaches the brain

In general all taste receptors bind specific molecules, which initiate an intracellular signal cascade leading to neurotransmitter release. Following neurotransmitter release, the chorda tympani, glossopharyngeal and vagal nerves transmit taste information to the brain. Two complex mechanisms have so far been identified in this transmission system.

These are ion channels and G-protein coupled receptors. Ion channels translocate ions across taste cell membranes and directly alter the ion balance which provokes neurotransmitter release.

G-protein coupled receptors act like switches in the membrane. On receiving a signal on the outside of the cell they 'notify' the interior, which responds by a chain of chemical reactions leading to release of a neurotransmitter. The food borne ligands (signals) that generate specific taste sensations have distinct biochemical properties. In each case, a metabolic consequence is also linked to the information sensed by these receptors.







Alzheimer's disease and the future of nutritional approaches for improving cognitive functioning in the elderly

(See also Food & Nutrition Communication, January 2007, Good Food for Healthy Ageing)

Whey protein stimulates **serotonin** synthesis and may improve neurotransmission. A better level of the neurotransmitter serotonin can help in the treatment of mood problems, mild depression, stress, pre-menstrual complaints and sleep problems. Compared to other major neurotransmitter systems, the serotonergic system is relatively easily modulated by dietary means. Whey protein is very interesting from this point of view.

Omega 3 fatty acids are believed to enhance performance of elderly people with mild cognitive impairment (MCI).

More severe impairments include dementias such as Alzheimer's disease (AD). This condition was first described over a hundred years ago. It features a gradual degeneration of the brain in plaques and tangles of proteins, together with a significant loss of neurons, and is characterized by severe memory loss and behavioural changes. Despite extensive research, little of therapeutic value has been clearly established – in other words - there is no cure yet. One hypothesis has been that AD is caused by a dysfunction of the central cholinergic system - hence the therapeutic use of drugs that inhibit the enzymatic breakdown of acetylcholine. The effect of these drugs is to delay the progression of the disease to some extent. Nutrients and nutraceutical compounds have also been advocated based on this hypothesis, but with little demonstrable positive effect. Other hypotheses point to a range of contributing factors such as age-related increases in oxidative stress and inflammation.



Recently however, brain imaging studies have revealed deficits in glucose utilisation in AD patients. These deficits occur early on in the disease before irreparable anatomical damage has occurred. This suggests a **dysfunction of the mitochondria**. When mitochondrial energy metabolism functions poorly, and leads to an imbalance of neuronal calcium, this can set off a programme of cell death (apoptosis). Research is now looking into stimulating mitochondrial function with vitamins A,B,C and E, co-enzyme Q, lipoic acid, carnitine, creatine and trace elements.

Oxidative damage also precedes plaque formation, and plays a central role in the development of the disease. It has been suggested that oxidative stress might trigger a vicious circle of increased production of reactive oxygen species, or free radicals, leading to neurodegeneration. The evidence has triggered a flurry of research into antioxidant treatments, including vitamin E, alpha lipoic acid, flavonoids/polyphenols, melatonin, ginkgo biloba, garlic and curcumin.

Time will tell. Animal studies are promising, but clinical evidence of the effectiveness of these treatments remains weak and needs further study.

Good news about Coffee

Up to recently it was thought that the main effect of caffeine was that it competed with adenosine, a sleep-inducing molecule, and therefore kept you awake longer. New evidence from a 10-year longitudinal study [6] recently published in the European Journal of Clinical Nutrition demonstrated that caffeine from coffee does much more than keep you awake; it actually reduced cognitive decline. In this study the apparent, optimal dose was three cups of coffee per day. Caffeine was proposed to stimulate certain neurons that protect against neurotoxicity. Since so many elderly people suffer cognitive decline, these findings could lead scientists to discoveries with considerable public health benefits.

Mens sana in corpore sano?

According to some research from Finland, by the age of 60, maximum physical force is reduced by about 50%. If mental acuity attention decreases in similar proportions, the impact of this becomes very clear. Even if not as dramatic as 50%, the speed of information processing and response in the brain shows a clear-cut, though gradual reduction with age.

Road traffic accident records in Finland attest to slow-reflex, age-related factors as primary causes of driving accidents (notwithstanding this country's remarkable rally drivers). The data is probably just as true in any other country.

Brain imaging studies reveal another effect: central inhibition processes can be impaired, leading to apparently reckless decision making. Also in the older brain, more areas are activated to perform tasks than in the younger brain, thus affecting the general topography. This 'recruitment' of other areas is thought to be due to the need to compensate for impaired areas. In high-performing elderly subjects new neuronal networks have been shown to occur in order to re-route around slow areas. But all being said, performance data and neurobiological evidence for age-related changes in information processing are complicated by a broad range of moderating factors including individual variability.

An important factor in the context of nutrition seems to be the psycho-physical state of older people which confirms the motto *mens sana in corpore sano*. **Physical training improves both physical and cognitive functioning** in the elderly. The fact that a better metabolic situation for the brain is one of the consequences of physical fitness opens interesting options for nutritional interventions.



Human cognitive assessment – difficult methodology

Cognitive functions [7] can be roughly grouped into executive, memory, attention, perception, psychomotor functions and language skills.

Because of their scope of action, interaction, modulation by other factors such as mood, mental energy physical discomfort etc., cognitive functions, and changes to them, are notoriously difficult to assess. Cognitive functions enable us to perceive evaluate, store, manipulate and use information from external (environmental) and internal (experience, memory, conceptual) sources to respond to cues.

Each function can be further subdivided according to auditory, visual, verbal, spatial and abstract procedures. It is extremely difficult to design functional tests with any degree of accuracy or consistency in the results from which to draw valuable conclusions, simply because of the huge number of variables that can affect performance at any one time. Among these the presence of fatigue, hunger, changes in mood and motivation, emotions such as fear, trauma, age, the effects of psychoactive compounds, noise, bad lighting, and extremes of temperature. There is no single, international gold-standard test, because there is no single, standard group of people to be tested.

So how should we measure nutrition-induced improvements in memory? [7, 8]

There is a basic distinction between declarative memory, (retrieval of name or phone number of someone), and non-declarative memory (such as how to ride a bicycle). As we all know, it is the declarative memory that is the first to go as we age. In memory tests used to assess a nutritional intervention, the methodology must be very carefully custom-designed for the population being studied. However, if an ability to identify groups at risk for Alzheimer's disease or other types of dementia can be developed, this will be of great interest to functional food development.



Specific performance deficits that have been associated with deficient nutrient intakes can be useful for trials of that particular nutrient, but not for the population as a whole. The point we made earlier in this article with regard to iron is an important one. There is a major difference between the impairment of brain function caused by a nutrient deficiency and improvement in that function by higher levels of that same or similar nutrient. A flat tyre causes immediate impairment in the performance of a car that can be completely returned to normal by replacing the tyre. However putting more air in the tyres or more tyres on the car does not make the car go better or faster.

The most important barrier to advancing our understanding of the role of diet in brain functions is the lack of quantitative measures of brain function itself.

Conclusion

The potential for good diets to improve brain functions is greater than we previously thought. Good diets can be learned and reinforced and healthy food can be delicious. It is especially critical to long term health of the brain and its functions to consume all the essential nutrients in the required amounts. It is also vitally important to avoid adverse metabolic conditions such as the metabolic syndrome and diabetes.

Many questions remain to be answered in detail, for example:

- *How can cognitive performance be improved by food in young and older adults and in children?*
- *Which are the irreversible pathways in brain development and cognitive age that are affected by nutrition or malnutrition, and which are the reversible ones?*
- *What is the potential for nutritional solutions to problems in brain functions versus pharmaceutical solutions?*
- *What practical, efficient nutritional ingredients might improve cognitive performance?*

Through its own research as well as the creation of two chairs in Nutrition and the Brain at the EPFL, the company demonstrates its ongoing commitment to the future of nutrition knowledge in general and of the brain in particular.

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Good Food, Good Life

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