final report

Project Code: D.MHN.0300

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Date published: November 2010

PUBLISHED BY
Meat and Livestock Australia Limited
Locked Bag 991
NORTH SYDNEY NSW 2059

Nutrition and cognition review

Meat & Livestock Australia acknowledges the matching funds provided by the Australian Government to support the research and development detailed in this publication.

Chapter E: Essential fatty acids

Executive summary

Long chain fatty acids make up a significant proportion of the rich lipid content of the nervous system. They play a crucial part in structure (for example in phospholipids) and function, both directly and through their eicosanoid and related metabolites. Their most prominent roles relate to membrane fluidity, but their influence extends well beyond this, for example to regulate neuronal functions, including neurotransmission, apoptosis and neuronal growth and hence neuronal plasticity, as well as having a profound influence on the developing nervous system.

Because of limitations in human capacity to elongate and desaturate LCPUFA, they are an essential nutrient whose supply appears to be sub-optimal in the diet of modern, developed countries. As well, the modern diet has led to imbalance between the two families of LCPUFA, ω-6 and ω-3, generally in the direction of decreased ω-3:ω-6 ratio. Supplementation of LCPUFA has a direct effect on tissue status, including within the central nervous system, although this limitation in enzymes means that appropriate balance between supplement components is important.

A wealth of observational data supports the notion that LCPUFA status is associated with development in infancy and into childhood, with mood states and with both healthy and abnormal cognitive aging.

However, despite a similar wealth of clinical trials, we currently lack definitive evidence to support the use of LCPUFA supplements in these situations. This stems in significant degree from a high level of heterogeneity between studies, due to many of these trials being small in number and diverse in design.

Nevertheless, the evidence that we do have allows the following conclusions:
1. A cognitive benefit can be expected from maintenance of appropriate LCPUFA status in preterm infants, particularly in relation to visual acuity and to a lesser extent neurodevelopmental indices. That evidence is sufficient to have lead many organisations to recommend that certain minimum levels of LCPUFA should be present in infant formula.

2. The evidence supporting their use in relation to clinical depression and for schizophrenia is interesting but requires larger trials.

3. The hypotheses that LCPUFA might help with other psychiatric conditions or mood states, or slow cognitive decline, all remain unproven.

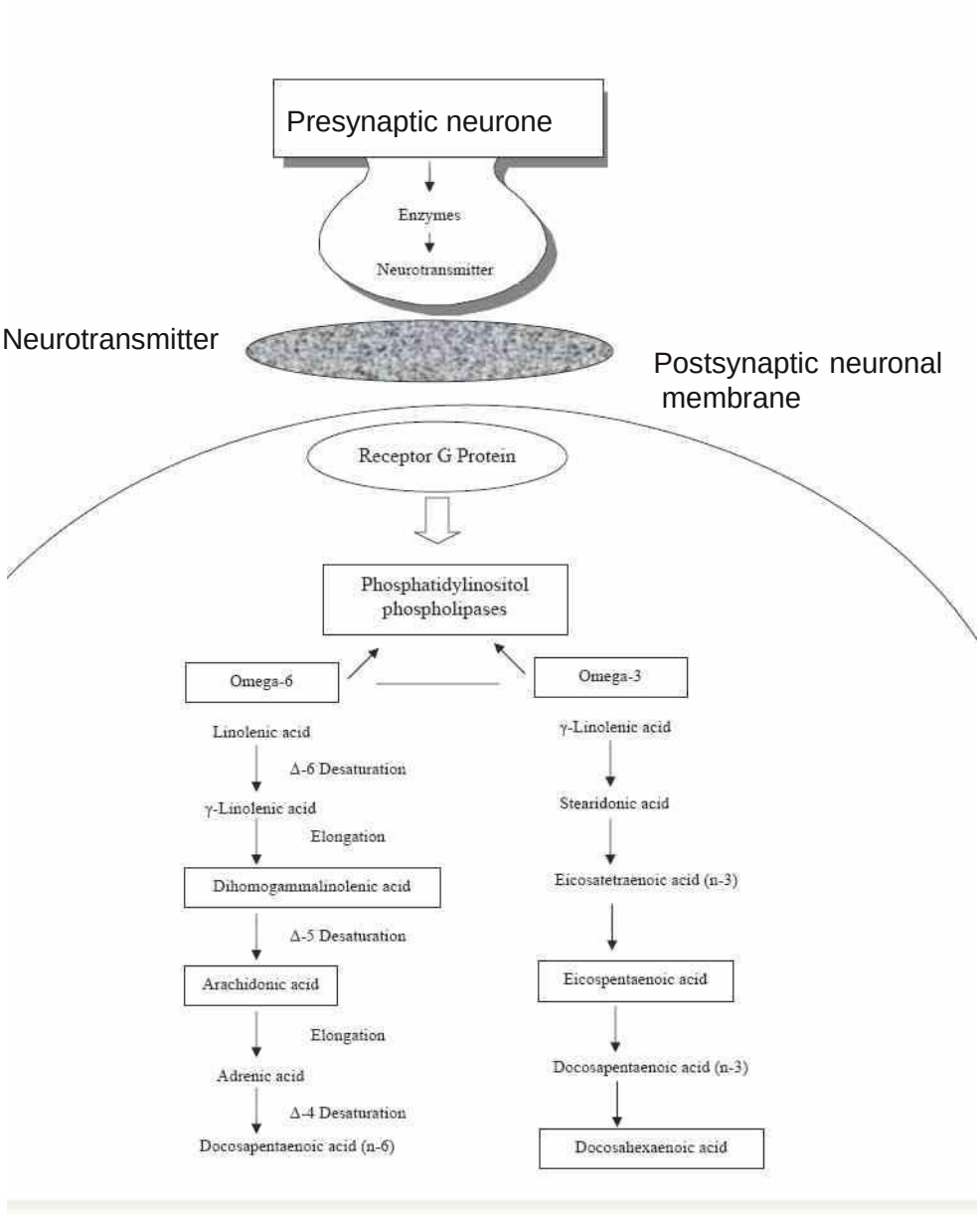
Physiology

The human brain is nearly 60% fat (by dry weight), being extremely rich in both lipid and fatty acid binding proteins. Apart from adipose tissue, the brain has the highest concentration of lipids of any organ. The principle fats are complex polar phospholipids, along with sphingolipids, gangliosides and cholesterol. The main fat component of glycerophospholipids is polyunsaturated fatty acids (PUFAs), which make up about one third of the brain lipid content. Within that family the major compounds are long chain fatty acids (LCPUFA), at the longer chain end of the desaturation-elongation pathways, in particular arachidonic acid (AA, 20:4) and docosatetraenoic acid (22:6) on the ω-6 pathway, and docosahexanoic acid (DHA, 22:4) in the ω-3 elongation pathway. (There are lesser amounts of the shorter chain PUFA, such as arachidonic).

In terms of specific brain phospholipids, AA is mostly found in phosphatidylcholine and phosphatidyl-inositol, DHA in phosphatidylethanolamine and phosphatidylserine. In terms of anatomical distribution, the proportions of DHA and ω-6 are about equal in the cerebral cortex, with a predominance of ω-6 in the white matter.

These fats are incorporated into and become crucial components of membranes within the brain and retina (which has the body's highest density of DHA), where they have both structural and functional roles. They influence membrane fluidity, signal transduction, gene transcription, structural integrity and recovery from injury. Their role in neurotransmission is on both sides of the synapse, affecting binding and release - see Fig.E1.

Figure E1: LCPUFA in neuronal signal transduction
(adapted from [15777112])



PUFAs affect the production and balance of eicosanoid metabolites (e.g. prostaglandins, leukotrienes) which can act as second messengers, as do adenylate cyclase and protein kinase A, levels of which are also increased by LCPUFA. They also have pro- and anti-apoptotic effects, for example mediated through the DHA metabolite neuroprotectin D1, as well as a role in inhibiting oxidant stress induced apoptosis 20329590, 20112300, 17392137, 17374644, 17302538, 16087970, 16048149, 15777112, 15263092, 10617981, C110.

Then of course there are potential indirect effects, for example on the cerebrovascular system, so that the list of potential mechanisms for LCPUFA to impact upon neuronal function and hence cognition becomes a long one. These are summarised in Table E1. It is also theoretically possible that they could impact neurodevelopment through boosting overall infant growth, but that is outside the scope of this review.

Table E1: Possible avenues for ω-3 LCPUFA to impact on neuronal function 19672626

Cerebral development
Development of vision
Component in neuronal membrane phospholipids
Effects on neurotransmitter systems
Regulation of corticotrophin-releasing hormone
Inhibition of protein kinases
Modulation of heart rate variability via vagal mechanism
Improved cerebral circulation and oxygen supply
Prevention of neuronal apoptosis
Influence on energy exchange
Influence on neurite growth
Regulation of gene expression Anti-inflammatory effects

Diet and deficiency

Because humans lack certain desaturates that would enable the ready interchange between ω-3 and ω-6 pathways, the balance in dietary intake between their dietary precursors (e.g. linolenic vs linoleic acid) is a determining influence on the eventual concentration of these LCPUFA in brain tissue and therefore of neural membrane structure and function 19214053. This is never more so than during foetal life and infancy, when the brain is developing. During pregnancy, around 600 gm of PUFA will be transferred to the foetus, a good deal of it during the final trimester. This process continues in infancy, aided by the LCPUFA content of breast milk. Overall, the majority of brain DHA is accumulated during the time from the third trimester to 2 years post-natal. This is certainly true of the hippocampus, and there is animal evidence to suggest that there is an ideal DHA concentration range for optimal neurite outgrowth, neuronal differentiation and synapse formation in this area during brain development. LCPUFA are also particularly critical for the retina 20233652, 18296333, 16048149, 15129302.

Animal-based experimental low LCPUFA diets during that time produce offspring with widespread neurodevelopmental defects, involving both neurones and supporting cells (astrocytes, oligodendrocytes etc.), depleted numbers and functions of monoaminergic neurotransmitter cells, abnormal retinal structure and function, and impaired learning, memory, visual attention and a range of other cognitive tests as well as changes in behaviour. In rats, for example, experiments have shown a direct relationship between LCPUFA content of the diet and neurotransmitter systems, such as changes in transmitter receptor binding and density. On the whole, but certainly not in every case, some restoration of cognitive function may be seen when LCPUFA status is replenished 20112300, 17374644, 1630730, 16087970. Insight into the impact of severe LCPUFA deficiency in human neurodevelopment is offered by the rare genetic disorder known as Zellweger syndrome, in which massive brain DHA depletion is associated with severe mental retardation. The brain damage is however, partly reversible with DHA supplementation (or indeed by the Lorenzo's oil made famous by a Hollywood movie, which was designed to treat another disorder of brain PUFA handling

known as adrenoleukodystrophy) [17408531, 18983586].

In later life, it appears that the brain's ability to synthesise DHA from shorter precursors diminishes with age, as indeed does the activity of desaturases in the liver. Broadly speaking LCPUFA concentration in the human cortex increases to age 18 years, and then decreases with aging [17302538, 11704343]. At the same time, some signs of aging cognition, such as decreasing hippocampal synapse density, have been partly reversed by DHA supplementation in animal experiments [20233652, 15129302].

A side-light to this discussion is the hypothesis that increasing availability of LCPUFA in the human diet (principally through gaining access to sea food) has contributed significantly to the enlargement of the human brain over evolutionary time scales [20112300, 18763477, 17408531, 17160979, 16828044, 14527626, 10419087], though this has not been universally agreed [16869985]. On a much shorter time frame, current Western diet is characterised by a reversal of what is thought to be the long term healthy dietary proportions of longer chain to shorter chain PUFA and ω-3 to ω-6 LCPUFA, in favour of the former in each case. Given the limited capacity of the elongation/desaturation pathways in humans, (and allowing for the absence of hard and fast "normal values" either for dietary intake or laboratory measures), the expert consensus is that significant proportions of the population have sub-optimal or marginal LCPUFA status, and that when this is further compromised (for example in pregnancy or old age), clinical manifestations of deficiency are likely [19339384, 19214053, 15802681, 15777112, 10799400].

Another important point is that supplementation with LCPUFA is readily reflected in corresponding changes in the concentration the supplements and their desaturated, elongated metabolites, in the tissues that take it up, including in blood and membranes of the body. Exactly what balance of LCPUFA will be brought about by a given supplement will depend, amongst other things, on the capacity of the enzyme systems involved in the chain lengthening process. This certainly applies to the brain [20112300].

Observational studies

Unlike many other areas of nutrition and cognition, when it comes to LCPUFA there are a substantial number of human clinical trials in addition to a great many observational studies. Around 200 human observational studies were considered for this chapter, and nearly the same number of clinical trials. Given the much greater import of trial data over observational, it is most practical to summarise the observational studies through the conclusions of expert reviewers, rather than to detail the individual papers.

It is convenient to divide the topic into the areas of: infancy, childhood, adults, aging (including dementia) and psychiatric, neurodevelopmental and related disorders.

Infancy, childhood

Three reviews have considered observational associations between measures of LCPUFA status during pregnancy or infancy and subsequent cognition in the infant up to age 7 years. The first was published in 2009 (to underpin recommendations on ω-3 LCPUFA intake in relation to neural development in the first two years of life). It identified seven epidemiological studies and concluded that they "linked low intakes of fish...in pregnant women, low blood levels of DHA in pregnancy or in infants at birth, and low breast milk DHA to lower scores on tests of mental, motor and visual system development in infants, with the effects extending into later childhood" [19214053].

The second review was published in 2010. It tabulates eight observational studies, of which only three are duplicated in the first review. It includes one study in teenagers, comparing their fish intake at age 15 years with their cognitive performance at 18 years. All but one study reported at least one positive association [20188533].

The third paper from 2009 tabulated twenty studies, four of eleven papers found a positive relationship with cognitive outcomes, nine from eleven studies with visual acuity (obviously there was overlap) [19505812].

Adults

This has not been well covered in systematic reviews, as there are few studies to consider. Serum DHA was correlated with tests for non-verbal reasoning and working memory (after adjustment) in 280 American adults aged 35-54 years [20181791]. On the other hand, baseline DHA was not associated with cognitive tests over 22 weeks in 54 adult women (although it was linked with a slower learning curve for one test) [17317131]. Amongst Seventh Day Adventists, the reported pattern of links between specific PUFA

intake and better mood cannot be easily separated from any number of confounding factors associated with vegetarian dietary practice [20515497].

Cognitive aging, (including dementia)

A review from 2008 cited six cohort studies, all of which showed a link between cognitive health and fish or ω-3 intake in the elderly [18296333]. (Four of these had already been included in an earlier review from 2006 [16340205]). The most comprehensive systematic review was published in 2010 and focused just on fish/PUFA intake and dementia or cognitive decline. From sixteen data sets involving over 27,000 subjects (with some overlap), all but one showed a protective effect - see Table E2 [20396634].

Table E2: Observational studies on PUFA intake and dementia/cognitive decline (N=16) [20396634]

	Study	n	Dietary var.	Outcome	Notes
9392577	Rotterdam Study, Netherlands	5,386	Fish	+	
12499483					
11201991	Canadian Study of Health and Aging (CHSA)	84	LCPUFA	+	X-sectional
14624027		65	LCPUFA	+	X-sectional
19474137		663	LCPUFA	NS	
12399342	PAQUID Study, France	1416	Fish	+	
17998483	Three-City cohort study, France	8085	Fish	+	ω-6 higher risk but only in non apoE4 carriers
12480746	Japan	89	LCPUFA	+	X-sectional
12654166	Dublin, Ireland	193	LCPUFA	+	X-sectional
12873849	Chicago Housing and Aging Project (CHAP)	815	LCPUFA	+	
16216930		3718	Fish	+	
16275829	Cardiovascular Health Cognition Study (CHCS), USA	2233	Fatty fish	+	Only in non apoE4 carriers
17101822	Framingham Heart Study, US	899	LCPUFA	+	
17413112	Atherosclerosis Risk in Communities (ARIC) study,USA	2251	LCPUFA	+	Cognitive decline
17413117	Zutphen Elderly Study, Netherlands	210	LCPUFA	+	Linear relationship, cognitive decline
19262951	Older People And Long-chain PUFA (OPAL) Study, England	867	LCPUFA	+	Cognitive decline
18258638	Birth cohort, Scotland	113	LCPUFA	+	Cognitive decline, only in apoE4 carriers
		27,087			

Outcome: + = protective association against cognitive decline/dementia, NS = no signif. association
X-sectional: Cross-sectional, case-control, rest are prospective for incident dementia, except those shown as “cognitive decline”.

A review from 2006 identified five observational studies on fish or ω-3 intake and age-related macular degeneration, three of which found significant protective associations, one did not and the other was not powered to do so [16841859].

Psychiatric, neurodevelopmental and neurological disorders

A 2009 review found only a little, inconsistent evidence on links between fish oils and dyslexia, motor coordination or autism [19339384]. A 2009 review found six of eight studies showed a link between ADHD and LCPUFA [19549202]. There is some evidence of inefficient conversion short to long chain PUFA [10617991].

A 2008 review reported that in 8 out of 11 studies on the relationship between depression and fish or ω-3 PUFA dietary intake there was a protective link [19079852]. A formal meta-analysis on 14 studies using tissue PUFA assays on 648 cases and 2,670 controls, from various backgrounds, found a protective association for both EPA (z=2.85, 95% CI: 0.06-0.31, p=0.0044) and DHA (z=3.68, 95% CI: 0.16-0.56, p=0.0002) [20452573].

There is very little data on the relationship between LCPUFA and these conditions in children or adolescents [C182]. Four studies on schizophrenics were cited in a 2006 review showing lower red cell ω-3 PUFA but, according to the authors, these results were open to confounding influences [17194275]. Of possible relevance to the role of LCPUFA in myelination, a half dozen studies linking multiple sclerosis to reduced LCPUFA were summarised in a 1995 paper [7598049].

Human clinical trials

A substantial number of clinical trials have been conducted in this area, particularly on infants, which is understandable given the premise that conventional formula has less LCPUFA than breast milk and that there is strong commercial interest in making available (more expensive!) LCPUFA enriched formula. The trials have allowed a goodly number of systematic reviews and formal meta-analyses, around which this section is based.

Infants

Two Cochrane meta-analyses have looked at LCPUFA supplementation in newborns. One dealt with preterm infants, the other with term babies. This is an important distinction, because the time course of LCPUFA brain accumulation being as was described above, preterm infants are likely to be borne with sub-optimal stores. Indeed, a recent report based on brain autopsy findings from infants who died in the perinatal period up to 2 years of age has confirmed just this vulnerability to PUFA imbalance [1532827].

Ppreterm infants, a Cochrane meta-analysis was published in updated form in 2008. Fifteen randomised, controlled trials involving supplemental feeding with LCPUFA were included, given to a little under 1,900 subjects, the latest paper being published in 2005. There was no consistent effect on visual acuity or neurodevelopment [18253973]. A later meta-analysis with similar focus published in 2009 included 10 trials on 1,405 subjects. All but one of these trials (from 1996, n=43) had been included in the Cochrane analysis. The only cognitive effect noted was a small increment in mental development score, mostly based on just two trials. Their conclusion was that: “further work is needed” [18400714]. An earlier 2000 meta-analysis concerned itself with just five trials where the subjects were healthy preterm infants and the outcome was visual resolution acuity. There was a significant positive effect of ω-3 supplementation [10835071].

Since that paper, the 18 month follow up on mental development index (MDI) and the 4 month follow up on visual acuity have been published from an Australian trial which compared high with standard concentration DHA enteral feeds in 657 premature infants. There was a significant benefit to visual acuity and (in girls only) to MDI [19141765, 18842793]. Another trial from Norway also reported cognitive impact of DHA-AA mixture given to very premature (< 1500 gm) infants for an average of 9 weeks [18519483].

Term infants, A Cochrane review from 2008 collated fourteen trials on 1,719 subjects. Whilst one research group had reported some benefit on visual acuity and two groups on mental development, the majority of the well conducted studies did not find any impact from giving ω-3 LCPUFA [18253974]. A systematic review from 2009 considered twenty four trials, nine of thirteen did not report any impact on cognitive outcomes, six from sixteen none for visual acuity. The authors described the results as being “mixed, likely due to study design heterogeneity” [19505812]. In a 2003 meta-analysis, on the other hand, fourteen controlled trials were looked at, of which seven had a specific cognitive measurement. The results were entered into a meta-regression, which was interpreted by the authors as indicating: “a strong and significant effect of DHA equivalent dose on magnitude of the visual acuity response” (at each of the different conversion rates from linolenic to DHA that had been assumed for the purpose of calculation) [14597910]. This is presumably a difference in analytical emphasis, since this review considered twelve of the same papers as the Cochrane paper, and eight as the systematic review!

A number of trials have reported their results since then. In an Italian study 1,160 healthy term infants were randomised to receive DHA or placebo supplementation for the first year of life. Although the DHA group sat without support on average one week earlier than controls, there were no differences in subsequent

milestone achievement dates [19056592]. By contrast, at the 4 year follow up results from an admittedly very small trial on 37 healthy term infants given LCPUFA until 12 months of age, the supplemented group exhibited significantly higher verbal and total IQ than controls [C483]. An RCT using various levels of DHA supplemented formula in 244 healthy term infants found significant improvements in visual acuity at 12 months of age, compared with control, but with no evidence of dose-response effect [20130095]. Another paper collated the cognitive outcomes at 9 months of age from three trials whose visual acuity results had been published much earlier. In each trial, DHA supplements were given to term infants at various stages during the first year of life. The combined result, based on 229 subjects, was that the LCPUFA group had higher scores for tests of means-end problem solving [19765006].

On the other hand, a recent RCT found an apparently adverse effect in term infants whose mothers were given DHA supplements during pregnancy. Those supplemented with DHA but no AA were more likely to have mildly abnormal movements at 12 weeks of age, compared with infants whose mothers received DHA+AA or control. The authors took this to suggest the importance of an appropriate DHA:AA balance. However the numbers were rather small (n=119 across the three groups) [19703327].

Children

There are no systematic reviews in children where the intervention lies entirely outside of pregnancy or infancy. But there have been several trials in which DHA supplements were given to healthy primary school children. In a small American study on 33 8-10 year olds, a mere 2 DHA doses over an 8 week period was associated with alterations in functional activity in cortical attention networks during sustained attention tasks [20130094]. A fish-flour spread given to disadvantaged South African 7-9 year olds for 6 months in a single-blind controlled design produced significant gains in verbal learning ability and memory, along with elevation of LCPUFA blood levels [19201180]. On the other hand, neither a well designed RCT over 16 weeks on 450 healthy similarly aged children from a mainstream school population in Wales, nor a trial over 8 weeks involving 90 10-12 year olds in England, could find any consistent effect on cognition from giving EPA/DHA [20171055, 19356306].

Adults

There are no meta-analyses or systematic reviews on cognition in normal adults. There have been several relevant trials conducted, one a recent randomised trial of ALA in pregnant women, the other following the fate of men with angina who were or were not advised to eat more fish. Neither however showed any effect on cognition [14643178, 12608739]. A mixture of essential fatty acids lowered the behavioural manifestations of test anxiety in an Israeli trial [16491653].

Elderly, cognitive decline and dementia

A systematic review was published in 2006 [16340205]. Apart from four observational studies, it found only a single 12 month intervention trial on 20 subjects in which DHA added to a nursing home's usual diet resulted in a significant improvement in two cognitive measures, but not past the 6 month point [10419198]. Since that time, a trial of 867 cognitively healthy older subjects who were given ω-3 LCPUFA for 2 years has reported that there was no cognitive decline in either active or placebo group, thus ensuring that the trial was unable to reach any conclusion about the potential to protect against such decline [20410089]. Neither of two levels of EPA/DHA supplementation given to cognitively healthy elderly for 26 weeks in a Dutch trial had any cognitive impact [18678826]. On the other hand, LCPUFA given as part of a multi-nutrient supplement (along with B vitamins and antioxidants) did improve memory in mildly Alzheimer's patients in a different Dutch trial, as did a DHA and lutin combination in a very small RCT on older American women, and EPA/DHA in another American trial on 485 elderly subjects over 6 months [20129316, 18510807, 20088810].

Psychiatric, neurodevelopmental and neurological disorders

A meta-analysis published in 2010 identified thirty five randomised trials (up to April 2009) on 842 subjects in which ω-3 supplementation was given and measurement of depressed mood was an outcome.
The clinical context included patients with major depression, bipolar disorder, post-natal depression, schizophrenia, Parkinson's disease and no underlying diagnosis. The pooled standardised difference (intervention to placebo) of the twenty nine trials that were suitable for pooling was 0.10 SD (95% CI: 0.02-0.17), but with strong evidence of heterogeneity and suggestion of some publication bias. They concluded that the evidence provided "some support of a benefit...in individuals with diagnosed depressive illness but no evidence of any benefit in individuals without a diagnosis of depressive illness" [20130098].

Another meta-analysis from 2009 looking at virtually the same type of trials identified twenty eight of them.

Remarkably only nine of those studies were in the other (2010) meta-analysis, yet their conclusions were very similar - the pooled data showed a beneficial effect (SMD=0.29, 95% CI: 0.12-0.46, p<0.001), more so in those with clinical disease, but with significant evidence of heterogeneity and publication bias. Unlike other first review, they also found evidence that EPA rather than DHA was the effective LCPUFA in this application [20439549].

A third meta-analysis looked at a slightly different question - the use of ω-3 LCPUFA in mood disorders, rather than its effect on mood in subjects not all of whom had mood disorders. The authors identified twenty one trials, including six not in either of the two reviews cited above. Thirteen were suited for formal meta-analysis, which showed a significant positive effect for depression (n=554, SMD=0.47, 95% CI: 0.2-0.92, p=0.07) with some dose-response (r=0.5, p=0.04) but not for mania. They concluded that: “The available evidence suggests that ω-3 fatty acids are a potential treatment of depressive disorders, but not mania. The unexplained between-study inconsistency and imprecision of the pooled estimates mitigate this suggestion” [19752840].

A Cochrane meta-analysis from 2008 focused just on bipolar disorder could not find sufficient evidence in the five trials considered to justify any conclusion [18425912]. On the other hand, a fifth meta-analysis in 2007 analysed ten studies (n=329) but concluded, granted the usual comment about heterogeneity and publication bias, that there was evidence of a therapeutic effect for depressive symptoms in both a primary depressive and a bipolar diagnosis [17685742].

A Cochrane meta-analysis updated in 2009 considered only schizophrenia, pooling results from eight trials involving 517 subjects (three trials not included elsewhere). They found evidence that ω-3 LCPUFA supplementation reduces the amount of neuroleptic medication required and improved mental state, but overall felt that the evidence was not convincing [C488].

A major systematic review and meta-analysis from 2005 looked at twenty seven intervention studies on ω-3 LCPUFA in relation to mental health. Incredibly, sixteen of the papers had not been included in any of the other five meta-analyses! It concluded (after taking into account observational studies as well) that: “Overall, other than for the topics of schizophrenia and depression, few studies were identified. Only with respect to the supplemental treatment of schizophrenia is the evidence even somewhat suggestive of omega-3 fatty acids’ potential as short-term intervention” [C459].

Several smallish trials have been published since these reviews were conducted. For example, one showing mixed results from increasing doses of DHA in depression, the other reduced anger and anxiety in substance abusers [18539007, 18060675].

In total, we can draw on no less than seven meta-analyses involving fifty seven trials. It is notable how similar their conclusions were - as a chorus they all recommend that larger scale, good quality randomised, controlled trials are now needed to confirm the status of ω-3 LCPUFA supplementation for depression and other psychiatric indications.

Conclusion

That conclusion could be echoed for the entire area of LCPUFA and cognition. That they play a vital role in the architecture and function of the nervous system is indisputable, and this applies both to neurodevelopment and aging. The most convincing evidence for clinical application at the present time is for visual acuity and possibly some developmental benefit in supplementing preterm infants - this would now seem prudent to apply in clinical practice. Certainly, from both an individual and a public health perspective, there is every reason to ensure that all formula fed infants, whether preterm or term, receive an adequate supply of LCPUFA in their diet, as should mothers during pregnancy and breastfeeding. Indeed, many expert organisations (including FSANZ) now do recommend or require that certain minimum levels of LCPUFA should be present in infant formula [C480].

The evidence supporting LCPUFA use in relation to clinical depression and for schizophrenia is interesting but requires larger trials, whilst the hypotheses that LCPUFA might help with other psychiatric conditions or mood states, or slow cognitive decline, all remain unproven.

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Chapter E2: Other fats

Executive summary

Cholesterol is essential for brain development and function, both for structure and function. There is reasonable epidemiological evidence that low serum cholesterol is associated with depression and suicide, possibly violent suicide in particular.

The preponderance of studies also suggests that low cholesterol is associated with cognitive decline and particularly with Alzheimer's disease and all-category dementia, but not with vascular dementia in particular.

In neither case, however, are the studies entirely consistent, or the pooled effect large. Nor is it possible to tell if this is a causative relationship.

Some studies have shown that an excess of saturated fat, and of trans-fat, may be associated with adverse cognitive effects, possibly including through some impact on insulin resistance. They are not conclusive.

Dietary gangliosides are required for brain health and are present in breast milk, for example, but this is a rather unexplored area in cognitive neuroscience.

Physiology

Many of the things that have been said about the neurophysiology of LCPUFA in the preceding chapter can also be said of cholesterol. Specifically, that it is a core component of the central nervous system, being a major structural element within cell membranes, involved in neurotransmission and important second messenger systems. Such systems have been thought to be involved in the mechanism of action of antidepressant and other mood stabilising drugs [19828089, 19321568, 15664301]. Also like LCPUFA, the cholesterol concentration in human milk is greater than that in conventional baby formula and it is interesting that a meta-analysis of seventeen studies showed that breastfed babies continue to have lower serum cholesterol values in later life than formula fed [19321568, 18689365]. Hence it is a fair question to ask whether abnormalities in cholesterol metabolism and status affect cognitive health.

Unlike LCPUFA, however, it is not clear to what extent exogenous cholesterol is required by the brain to meet its needs, or whether it is reasonably capable of synthesising its own [19321568]. Another difference is that, from an epidemiological perspective, any negative influence on cognition from low cholesterol would have to be separated from the adverse impact of cerebral arterial insufficiency due to atherosclerosis associated with an elevated serum cholesterol. The hyperlipidaemic atherosclerotic state is also inflammatory, which could affect cognitive function. Another possible interaction is that alterations to LCPUFA intake could have an impact on lipid dynamics, although this will be mostly in relation to triglycerides, or the cholesterol intake in relation to overall energy `budget' [14622442].

Observational studies

This issue was given greater impetus with the observation, following on the widespread implementation of cholesterol lowering therapies for atherosclerosis prevention, of an apparent association between low levels of cholesterol and higher suicide risk [11819151]. A good many observational studies have therefore been conducted to address the question of whether there is indeed any link between cholesterol and mood disorders or suicide. A systematic review published in 2009 collated studies up to April 2008 into several tables, two of which are the basis for Tables O1 and O2.

Table O1: Observational studies on cholesterol and depression [19828089]

	Study design	Cases n=	Controls n=	Outcome	Sub-group(s) to whom this applies
8093404	X- sectional	1020		-	
8931915	Case Control	100	110	-	
9111854	Case Control	36	28	-	
10645328	Longitudinal	29,133		-	
11208367	X- sectional	102		-	
11022402	X- sectional	33		NS	
11933923	Longitudinal	114		+	
11939964	X- Sectional	186		-	
11959358	Longitudinal	47		-	Patients with anxiety, hostility, depression
12189257	Longitudinal	322		+	Non-responders to fluoxetine
12759558	Longitudinal	92		+	
15572853	X- Sectional	987		+	
14675744	Longitudinal	92		NS	
C494	Retrospec-tive	37		+ HDL	Patients with higher suicide risk
15820273	Longitudinal	109	59	NS	
18583011	X- Sectional	124		NS	
18547475	X- Sectional	145		-	Alexithymic patients
	TOTAL	**32,876**	**197**		

Outcome: - = lower cholesterol + = higher cholesterol associated with suicide

Table O2: Observational studies on cholesterol and suicide
(successful, attempted or contemplated) 19828089

	Study design	Cases n=	Controls n=	Group(s)	Out-come
10963796	X- sectional	25	27	Violent vs non-violent suicide	-
15272101	X- sectional	74		Suicide vs non-suicide anorexia nervosa patients	-
17360043	X- sectional	74		Manic depression and schizoid	+
7795448	Case Control	331	331	Parasuicide vs healthy	-
7864269	X- Sectional	650		Suicide vs non-suicide psychiatric	-
15306143	Case Control	149	400	Suicide vs non-suicide psychiatric vs healthy	-
11954543	Case Control	231	462	Suicide vs non-suicide psychiatric vs healthy	-
17270280	Case Control	27	27	Suicide vs non-suicide 1st.psychosis vs healthy	-
14999659	Case Control	10	34	Suicide vs non-suicide panic disorder vs healthy	-
19026260	Case Control	417	613	Suicide vs non-suicide psychiatric vs healthy	-
11223109	Case Control	12	6	Depression/suicide vs healthy	-
12056581	Case Control	111	62	Suicide vs healthy	-
12648892	Case Control	9	51	Violent vs non-violent suicide vs healthy	-
16263178	X- sectional	3237		Community subjects	NS
	TOTAL	**5357**	**2013**		

Outcome: - = lower cholesterol + = higher cholesterol associated with suicide

In looking at the results in detail, the authors concluded that, although not all studies have come to the same conclusion, the majority did find a relationship to suicide (and some to more violent suicide). There was less consistency in relation to depression and bipolar disorder 19828089.

In an earlier review from 2002, a formal meta-analysis was done, and found “a tiny but statistically significant increased risk of completing suicide. Individuals who have attempted suicide in the past have lower cholesterol levels, especially if they used violent methods for suicide. Cholesterol lowering studies, however, did not lead to a significant increase in completed suicide” 12374479.

Two more recent studies have reached mixed conclusions - one finding a link with attempted suicide in adults and the other not finding it in children and adolescents. Both had small samples 20299106, 20047063.

Association is, of course, not causation. It easy to imagine, for example, that people who are depressed or suicidal might decrease their dietary intake so as to decrease their cholesterol levels. There have been few controlled clinical trials specifically to address this question. In an RCT on 491 adults at risk for heart disease with elevated serum cholesterol who were given simvastatin or placebo, there was no difference in mood scores after an average of 3 years 8688757. The same outcome was obtained when comparing lovastatin with placebo in a trial of 209 hypercholesterolaemic adults over 6 months, and in comparing Mediterranean, low-fat and control diets over 12 weeks 10806282, 10806283. The issue of causation remains unresolved.

Cognition and dementia

Several studies have suggested an association between cholesterol and cognition. For example, in three studies on healthy adults, total serum cholesterol was negatively correlated with executive control and sustained attention in a sample of 46, with some sub-tests of cognition (after controlling for age) in a sample of 177, and with visuomotor speed (after adjustment for sociodemographic variables) in a sample of 4,110 subjects 18510808, 15277148, 9251158. However, there was no association with cognitive or academic achievement in 4,248 American school children from 6-16 years of age 19622240. In two of the RCTs using

cholesterol-lowering treatments that were mentioned above (in regard to mood), there was no impact on cognition [10806282, 10806283].

In relation to cognitive decline and dementia, a meta-analysis published in 2008 included 18 prospective studies over periods ranging from 3 to 29 years, on 14,331 subjects evaluated for Alzheimer's, 9,458 for vascular dementia, 4,793 for cognitive impairment and 1,893 for cognitive decline. The authors found consistent associations between elevated midlife total cholesterol and Alzheimer's or "any dementia", as well as for cognitive impairment, but not for late life cholesterol, for vascular dementia and only weak evidence for cognitive decline. There is also some suggestion of an interaction between these relationship and the well established risk factor related to ApoE lipoprotein genotype [18448847, 15668424].

Other fats

Completing the picture is evidence on the cognitive impact of other types of dietary fat. Some human and animal studies suggest that excess intake of total fat, or trans-fats has a detrimental effect on cognitive performance, including in healthy subjects, in relation to cognitive decline and recovery from traumatic brain injury. This may be in part because of an adverse effect on insulin dynamics. There is also a some evidence that dietary gangliosides (including sialic acid) are essential for neurodevelopment, including in humans, and they are present in human breast milk [19945473, 19336640, 19321568, 16257476, 15136684, 12770552, 12088740].

Whilst the evidence on these points is interesting, it is certainly not conclusive in terms of clinical application, and research on human dietary gangliosides and cognition is still a rather unexplored area in cognitive neuroscience.

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Chapter O: Other nutrients

Executive summary

As a highly metabolically active organ with a large amount of fat tissue, the brain generates a high level of reactive oxygen species as a by-product. For this reason it requires a finely titrated supply of **antioxidants**. The balance between pro- and antioxidant forces also comes into play in relation to cell apoptosis, which is an integral part of brain plasticity. Imbalance, on the other hand, is believed to be a core part of the process of brain aging and neurodegenerative disorders. The best evidence linking specific antioxidants with cognition is for vitamin E, and to a lesser extent flavonoids, selenium, and vitamin A. For none of these are there many convincing RCTs.

Calcium has a central role as a second messenger, and in the operation of calcium voltage-gated ion channels. An imbalance of calcium is believed to be part of a trinity of pathological processes that causes brain aging, along with mitochondrial deterioration and oxidative stress.

Vitamin D is involved in calcium homoeostasis, but also has a range of functions apart from this, for example in stimulating and regulating neuronal cell growth and vitamin D receptors are widely distributed throughout the brain. In clinical terms, there is an association between vitamin D deficiency and dementia and depression, but clinical trials do not yet prove that this is a causal relationship.

Magnesium is, along with potassium, the main intracellular cation in neurons, and as well is co-factor in hundreds of enzymes, which gives it a role in a wide range of functions: membrane integrity, protein synthesis, energy metabolism, maintenance of ionic gradients, smooth muscle tone, regulation of ion channels, calcium transport and regulation of cytokine production and secretion. Particularly important is its modulation of NMDA glutamatergic receptors, the main excitatory neurotransmitter system in the brain. Magnesium deficiency is a hyperexcitable state and magnesium supplements have been used for various such states, including epilepsy, eclampsia. It has also been used to treat depression and to limit damage from neurotrauma and stroke.

Vitamin K is a fat soluble nutrient involved in myelin synthesis and the early development of the CNS. **Copper** is required as a co-factor in antioxidant defense. **Sodium** and **potassium** are fundamental ions in maintaining the neuronal membrane's resting potential and through their flux across that membrane the transmission of nerve impulse. Whilst significant disturbance of the concentration of either is a potentially fatal condition which includes neurological deficits, the tight homeostasis over their tissue levels maintained by the body ensures there is little practical connection between dietary intake of these nutrients and cognition.

Iodine is a fundamental requirement for thyroid hormone production, which in turn is a fundamental requirement for the development of the brain. Iodine deficiency is widespread throughout the world, and mild to moderate levels of deficiency by no means uncommon in Australia, particularly in pregnancy. There is good reason to believe that this has cognitive consequences, and some good clinical trial evidence to suggest that correction of even the milder levels of deficiency will have cognitive benefit. This is one nutrient where the cognitive connection is both clear and practical.

A number of **trace elements** have in common a degree of essentiality in biological doses, but clear danger of toxicity from overdose, particularly when consumed from industrial/environmental sources in inorganic form. The best established from the cognitive perspective is manganese, others include vanadium, boron, and chromium.

Carbohydrate, as the readily available source of glucose, is required for energy supply to the brain, and a good deal of research has been done on the cognitive impact of glucose feeding. However, the clinical relevance of this in real life situations is not clear. The cognitive benefit of eating **breakfast** is much clearer,

particularly in nutritionally at-risk children, but this may also be because of collateral health benefits.

A substantial number of trials have been conducted on the cognitive effect - including on IQ - of giving **broad spectrum nutrient supplements** to various populations groups, including highly at-risk children in the developing world, the elderly, and those at no particular risk, for example healthy adults in Western countries. The broad thrust of results shows that a significant impact can result, but even more so than with the feeding of breakfast it is far from clear whether this is a direct effect on the brain, or an indirect benefit of the general improvements in health and wellbeing associated with the supplementation.

The relationship between cognition and **overweight** is replete with confounding influences, and it is necessary to exclude most of these from consideration of the simple question of whether an excess of fat tissue in itself affects cognitive processes. The answer is most likely yes, because obesity is an inflammatory state, and because of the neurophysiological roles of weight regulating hormones such as leptin. Although one would assume that people who diet to lose weight would be happy when they succeed, there has been some concern that weight loss may be associated with depression, particularly low-carbohydrate dieting (because of its connection with tryptophan and serotonin). However, the clinical evidence so far has not done much to confirm this.

Water is essential to brain health, and dehydration affects cognitive function. However, the experimental studies in which this has been established have generally used healthy, fit subjects in situations of heat and physical exhuastion, and those stresses may well have confounded the results. Whether cognitive deficit from dehydration is a practical concern to the average person in daily life has not been established.

A number of other nutrients and food-derived compounds have functions within the brain, but the evidence as to how to apply this in practice is lacking, despite various attempts to conduct supplement trials involving them . These include the mitochondrial co-factors and antioxidants **acetyl-L-carnitine** and **α-lipoic acid**, the antioxidant **ferulic acid**, the choline metabolite **lecithin**, and the carbohydrate based **gangliosides** (and their component compound sialic acid). It also includes **phytoestrogens**, for which brain chemistry is likely to involve both their antioxidant and oestrogenic effects. Unfortunately, even though the number of clinical trials is significant for some of these (e.g. twenty on phytoestrogens), the general case for those trials has been small samples and highly heterogeneous sample selection and methodology. This has limited our ability to reach strong, clear conclusions in regard to the practical cognitive application of any one of these substances.

This chapter provides a brief overview of a number of other nutrients that are not covered in detail because either the evidence for a significant clinical impact on cognition is weak, or it is very difficult to dissect from the influence of covariates, or has limited relevance to the general Australian population.

Antioxidants

Oxidative stress is present in many of the disease processes affecting cognition which have been mentioned in previous chapters as being associated with abnormal nutrient status, For example, hyperhomocysteinaemia, neurodegenerative diseases including Alzheimer's disease and other forms of dementia.

Although, as we have seen, the strength of the evidence on the causality of those associations is not always convincing, the fact that the diseases themselves are characterised by high levels of oxidative stress and elevated amounts of reactive oxygen species (ROS) is not in dispute. A good example is Alzheimer's disease and other forms of dementia, to a lesser extent cognitive decline in general [19376275, 17517043, 15265281, 15096701, 15096699, 11174040, 10681270, .10593298.] . Looking wider afield, oxidative stress seems to characterise the broader scope of pathology of which those diseases are examples, that encompasses neurodegeneration, neuroinflammation and mitochondrial deterioration [19721819, 17961149, 17306357, 17303344, 17051205, 11237183].

This being the case, there is obvious potential in those situations for the antioxidant nutrients that constitute the body's defence against oxidative excess to be used up at a high rate, and ultimately their status compromised, particularly where the patient is not consuming sufficient antioxidants in their diet. This would then leave the body open to unmitigated consequences of further oxidative stress from the original disease state. It might also expose the brain to any adverse effects that arise directly from the lack of the antioxidants themselves, if indeed there are any. Such antioxidants would include selenium, vitamins A, C and E, a variety of polyphenols and glutathione (a tripeptide which appears to be concentrated in glial cells and have particular importance to oxidant control within the brain, including within the brain's `immune cells', the microglia) [16115027, 10931173].

There is another side to this story, too, which needs to be taken into account. This is the physiological role that oxidative stress plays as a part of the normal cellular life cycle, for example in bringing about apoptosis, i.e. in programmed cell death, a process that is integral to neuronal rewiring and hence brain plasticity [15298006, 12749676]. Clearly, all in all a complex, interwoven picture.

Because of its high metabolic rate (using 20% of the oxygen while making up only 2% of the body's weight), and lesser capacity for regeneration than many organs, and because of its very high proportion of lipid, the brain has a particular susceptibility to oxidative stress. ROS have the capacity to damage the structural integrity of DNA and protein in ways that could easily lead to impaired brain function. Moreover, ROS can change set-points for signalling systems, which would be particularly impactful on cognition, as well as disturbing the homoeostasis and compartmentalisation of brain iron and calcium, either of which can be directly neurotoxic. Although there is some reduction in oxidative brain metabolism with aging, a progressive imbalance between intracellular ROS levels and antioxidant status develops with increasing years. [17517043, 15298006, 10931173, 6821143, C124].

So the potential is certainly there for oxidative stress to play a role in cognitive dysfunction. Even so, it is difficult to be sure whether the oxidative stress that is observed is the cause of the neuropathology with which it is clearly associated, the effect, coincident with it, or some combination of all three [17517043, 15298006, 15096700]. The same can be said of observational studies on cognition in relation to antioxidant nutrient status conducted in the elderly, the cognitively impaired and those with other diseases, since the potential for confounding in such situations is particularly high, for the reasons outlined in several earlier chapters (and there is no shortage of such studies, e.g. [19914330, 19158425, 18654878, 18614745, 18469254, 18320305, 17369607, 17325274, 17130689, 16799145, 16611085]).

The question of whether antioxidants have any specific function in cognition (apart from providing defence against ROS) may be a little easier to answer when looking at studies in animals and healthy human subjects. There is some evidence that antioxidant deficiencies can impair and supplements can improve cognitive and neuromuscular function, in animals both young and old [20187127, 19926923, 19640959, 19356316, 17537957, 16549472, 16194581, 16020519, 15682927, 14726220, C195, C137]. The best evidence is probably for **vitamin E**, which is not surprising because of its particular potency in protecting lipids from peroxidation [C124]. There are some rather rare

clinical hypovitaminosis E syndromes which are included amongst the 'nutritional neuropathies', a grouping that includes pellagra, dry beri-beri etc. Full blown hypovitaminosis E features some severe neurological symptoms involving the posterior column, spinocerebellar tracts, retina, and peripheral nerves. However, lesser degrees of neuropathology may be seen in secondary hypovitaminosis E, which can be due to disease such as cystic fibrosis, abetalipoproteinaemia, short bowel syndrome etc. The neurological manifestations may progress from hyporeflexia, ataxia, limitations in upward gaze and strabismus to profound muscle weakness, blindness and dementia. Some of these symptoms may be explained by a direct non-antioxidant function for vitamin E in cellular signalling, though others have asserted that this is purely the result of its anti-oxidant role in preserving the integrity of LCPUFA in neuronal membranes [20464573, 20183831, 19133328, 17913225, 17561088, 17324726, 12691170, 11245349, 9012278].

Another class of antioxidants for which there is a useful body of animal evidence is the **flavonoids**, as found for example in berries and other fruits. Research has shown that they have a beneficial effect on memory, including protecting against age-related deterioration. This may be via non-antioxidant actions, through impact on cell signalling and synapse function, improving local brain blood flow and scavenging inflammatory mediators and end-products, particularly at brain sites such as the dentate gyrus and hippocampus [20955649, 20158941].

Selenium is another antioxidant with some specialised functions within the brain. It influences the activity of glutathione peroxidase, which acts on the important brain antioxidant glutathione. It can help counter the neurotoxic effect of heavy metals such as mercury, cadmium, lead and vanadium, and can is important for proper CNS action of thyroid hormone [12751781, 11842884].

Vitamin A is interesting because retinoic acid, apart from its general role in regulating gene expression throughout the body, specifically affects neuronal signalling systems. These functions are particularly important during brain development, but there is also evidence that this continues to play an important role in the mature brain. Retinoid receptor proteins can be found within the adult cortex, amygdala, hypothalamus, hippocampus and striatum [16507818, 15882777]. And of course it has a specific function in vision. In animal studies, retinoic acid stimulates neurogenesis in the hippocampus [18941534, 18782483]. In humans, several observational studies have reported an association between lower vitamin A status (for carotene) and cognitive decline in the elderly [17389729, 16799145].

There is limited evidence on cognitive effects of antioxidant supplementation in healthy human subjects. When considering these results, one thing that should be borne in mind is many antioxidants (particularly the water-soluble ones) have limited absorption across the blood-brain barrier [11406187] and very few of the trials took measures of the extent to which they crossed it. Vitamin C had no effect on cognition over 12 months in an RCT of healthy elderly [C247]. Selenium improved mood in a few small trials, but not in all [19942640, 1873372, 18006208, 8717610, 8717610, C253, C204,]. But in much larger trials in subjects who were middle age and older, results have not been particularly encouraging. There was no difference in cognition between placebo and β-carotene given to 1,904 middle aged physicians over and average of 1 year, although there was some effect in the follow up of 5,956 subjects treated for 18 years [17998490]. In the very large Women's Health Study of nearly 40, 000 women ≥65+ years old, long term use of vitamin E over a decade provided no cognitive benefits [17159011]. In another large trial of older women, in this case 2,824 women with CVD or at high risk for it, vitamins A, C and E did not slow cognitive change, although there was an effect on the final cognitive score for the vitamin C sub-group [19451353]. It should however be pointed out that cognition was not the primary end point in these trials, and hence their methodology and the cognitive tests used may not have been optimally designed to detect a significant effect if there had been one.

There have been nearly three dozen trials using flavonoids, in healthy adults, post-menopausal women and older subjects, with active interventions including isoflavones or soy, flavonoids (such as L-theanine) that are found in tea and coffee, in chocolate and cocoa, grape juice and various other botanical products. More than 50 different cognitive tests were employed. Some trials showed a benefit on measures of memory, other cognitive functions or mood, some did not [C516, C515, C514]. A systematic review of fifteen of these trials (published in 2009, including studies up to 2008), concluded that the evidence was encouraging, but lacked methodological consistency across different studies, and that there was a need of further trials [19680703]. There is also some human data demonstrating that flavonoid supplements can increase cerebral blood flow [20357044, 16794460, C314, C126].

In interpreting the flavonoid data, it should be borne in mind that soy food and the isoflavones derived

from it are not only antioxidants but also phytoestrogens, i.e. they also have hormonal actions that may be entirely independent of the antioxidant properties. Hence, whilst it is convenient to group the trials together for consideration within this section, the question of the phytoestrogenic effects on cognition is briefly discussed in its own section later in this chapter.

There have been a number of trials of antioxidant supplementation in patients with established cognitive impairment, including Alzheimer's disease, but in many cases the antioxidant was combined with other nutrients or pharmaceuticals (e.g. vitamin E and donepezil [17452062, 16436560, 15829527, 12151908]), and there has been very little consistency in the type, dose and duration of the intervention or in other elements of methodology. There was a mixed result a trial on 341 Alzheimer's patients with improvement in some whilst others were made worse [19494439]. In another smaller trial (n=57), whilst there was no difference in any of the primary outcomes (one of which was severe dementia), the vitamin E group took longer to get there than placebo [9110909]. There was no positive effect in a reasonably large trial involving vitamin E in 769 subjects with mild cognitive impairment [15829527]. These latter two trials were the only ones that were found suitable for inclusion in a Cochrane meta-analysis on vitamin E and cognitive impairment from 2008, and therefore the authors' conclusion, as one might expect, was that there was no evidence of efficacy [18646084]. Other interventions have included ginkgo, curcumin, alpha-lipoic acid, arginine and N-acetylcysteine [18690838, 17982894, 18204357, 11673605, 10759111, 9447569, 9343463, C496]. Collectively these trials do not add up to much.

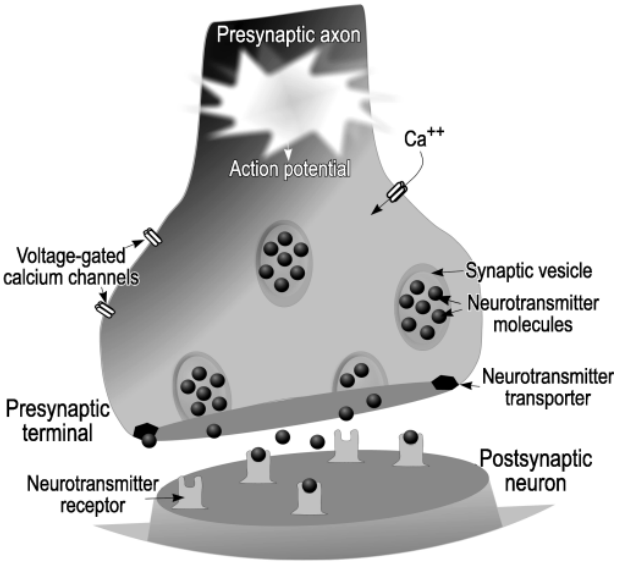
There is also a body of literature concerned with the antioxidant and other cognitive effects of the neuroendocrine hormone melatonin, its metabolites and precursors (such as N-acetylserotonin), on the synthetic pathway for melatonin that begins with the amino acid tryptophan. Part of this research concerns itself with the role of melatonin in protecting against neurodegeneration in conditions such as Alzheimer's disease [19857546, 17910609, 15207391, 12587715, 11141317, 10668422, 9745987, 2345536]. A Cochrane meta-analysis published in 2006 could find only three trials on melatonin for cognitive impairment and concluded that "There is insufficient evidence to support the effectiveness of melatonin in managing the cognitive and non-cognitive sequelae of dementia" [16437462]. Clinical trials since then focused on reducing agitation in demented patients and cognition in ADHD and insomniac children have not shown any clinical benefit [19155748, 17046034].

Calcium and vitamin D

Calcium

Calcium has a central role in signalling within cells throughout the body, particularly as a second messenger, thereby having effects on gene expression, cell growth, development, survival, and cell death. As we have seen, cell death is as essential to neuroplasticity as is cell growth. Within the nervous system, calcium has more specialised functions, as an integral part of the operation of the synapse leading to neurotransmission, and the mechanisms (such as sensitisation of NMDA receptors) by which long term potentiation occurs. For example, voltage gated channels allow calcium into the interior of the end bulb of a neurone as the nerve impulse reaches it, which stimulates synaptic vesicles to migrate towards the synapse - see figure O1**.** These signalling actions of calcium are modulated by what are known as `calcium proteins'. The rise in intra-cellular calcium concentration initiates a cascading sequence of changes,

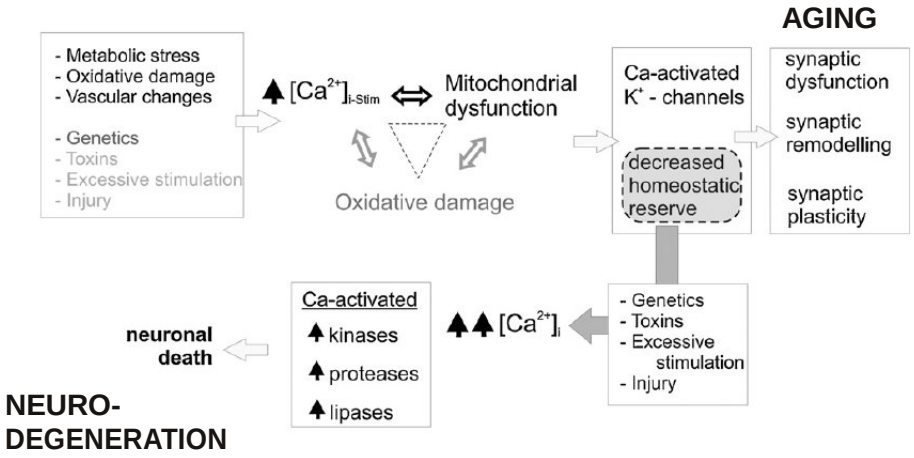
Figure O1: Calcium and neurotransmission [C497]



mediated by the calcium protein calmodulin, which in turn acts on the aptly named calcineurin, all of which is part of the mechanism of both rapid signalling and memory formation [20668007, 20045187, 19909276, 19455319, 19273181, 18817727 12655069]. It has been suggested that calcium and calmodulin together could potentially act as an anti- depressant by increasing the number of synaptic vesicles available for neurotransmitter release [11754827].

Calcium homeostasis is strict, and any weakening of it is associated with potential cellular damage, for example mitochondrial dysfunction and oxidative stress. This kind of dysfunction, including change in the operation of the calcium channels, is thought to be part of cognitive aging (as part of a pathological triad of abnormalities in calcium, mitochondrial function and free radical production) and other dementing conditions such as that seen in advanced AIDS - see Figure O2. The increase in amyloid deposition that is characteristic of Alzheimer's disease is also known to interfere with calcium signalling. Disordered homoeostasis affecting the glutamate-calcium cascade may also play a part in brain damage from insults such as trauma and stroke [20649555, 20045187, 19795132, 18583041, 12449809, 11000422, 7847672].

Figure O2: Calcium theory of brain aging (gray text describes factors not considered to be of primary significance in current models) [20045187]



Although the basic science is very strong, it is surprising how little good human data there is. There is no doubt that the symptoms of severe calcium deficiency (clinical hypocalcaemia) include cognitive impairment and mood disturbance, as well as neuromuscular irritability and cramps [10763903]. Psychiatric symptoms are also found in hyperparathyroidism [19807940, 19336505, 2458656, 2446670]. But outside of these clinical extremes there is only a scattering of observational studies linking calcium status with cognition, for example with cognitive decline in the elderly (but they showed contradictory findings), depression, premenstrual syndrome and other psychiatric disturbance [18808606, 17979900, 10763903, 9396014, 7862840, 8296774, 420907, 2046163]. Even these must be tempered by the possibility that calcium could be indirectly associated with cognition via its effect on hypertension and atherosclerotic arterial disease (generally thought to be a protective one) [20629479, 19083421].

Clinical trials are even scanter. In a randomised clinical trial on 293 women, those given calcium supplements during pregnancy had significantly less post-partum depression than those given placebo [C381]. A small number of other RCTs used calcium supplements for premenstrual syndrome, some with benefit on cognitive symptoms or mood, some not [19574172, 9731851, 8498421, 2656936]. Pharmacological agents that block voltage-gated calcium channels have also been proposed for treatment of mood and cognitive disorders, as well as other neurological conditions characterised by an imbalance between neuronal excitation and inhibition, such as chronic pain and epilepsy [19519559, 15347035, 10500866, 2165504]. However, this is well outside the scope of this review.

Vitamin D

In considering the role of vitamin D in cognition, it is obviously relevant to consider its effect in regulating calcium levels. But there has also been an increasing awareness over the last decade of the non-calcium mediated roles of this vitamin. These so-called extra-skeletal functions elsewhere in the body include immune function, and impacts on growth, cardiovascular disease, cancer, muscle function

and body weight [20629479, 20226390, 19940269, 18579197]. One way that these functions have been tracked has been through the distribution of specific vitamin D receptors within the body. These are found extensively throughout the brain, including in the prefrontal cortex, hippocampus, cingulate gyrus, thalamus, hypothalamus, and substantia nigra, some of which areas, coincidentally, are believed to be involved in memory and depression [15589699, C148]. Vitamin D deficiency in animal studies is associated with impaired differentiation of nerve cells and imbalance of growth and apoptosis factors. Knockout mice without VDR also show behavioural abnormalities. It remains unclear how vitamin D relates to neurotransmitters, such as dopamine [C148]. Vitamin D stimulates neurotrophin release, and may protect the brain against neurodegeneration by buffering antioxidant and anti-inflammatory defenses against vascular injury [19940269, 19494440, 19187703].

Many observational studies have investigated vitamin D status (or lower parathyroid hormone) in relation to cognition, particularly in the middle aged and elderly, as well as looking at the risk of cognitive decline and dementia. The majority reported a protective association. A systematic review published in 2009 found five observational studies on this topic that were considered suitable for inclusion (four cross-sectional, one case-control, most recent from 2008), involving just over 10,000 subjects [18503256, 17898524, 17258168, 17138809, 16283099]. The authors found the evidence unconvincing [19659751]. That is what one might expect, given that over 95% of the subjects were from just one study, which reported no significant associations.

However, nine further studies have been published since then (including one by the same principal author as the systematic review!) involving 9,592 subjects, including two longitudinal studies, of which eight had a protective association [19940273, 19940271, 19934619, 19794127, 19460797, 19397226, 19377013, 19336505, 19073839]. For example, vitamin D deficiency in a sample of 752 community dwelling women ≥ 75 years of age was associated with double the risk of cognitive impairment (adjusted odds ratio=1.99, 95% CI: 1.13–3.52, p=0.017) [19794127]. There have also been a number of observational studies linking vitamin D status with depression, including seasonal affective disorder, with the obvious possibility that this is related to the effect of lesser sunlight levels on vitamin D status) [19125208, 18458202, 17499448, C148]. However, a newly published analysis on 3,916 American adults from the national NHANES study did not find any association [20642877].

Human clinical trials are in short supply. An RCT on 441 overweight adults reported that those given vitamin D had significantly better depression scores after 1 year, compared with no improvement in the placebo group [18793245]. Whereas no improvement was seen in two trials of vitamin D in seasonal affective disorder, one on 250 adult women over 1 year, the other on 2,117 older women over 6 months [16554952, 8140183]. Future RCTs would be most welcome, particularly in those with demonstrated vitamin D deficiency and those at high risk of it (e.g. the elderly), and in patients with depression, particularly season affective disorder. Until we have those, it is too early to reach any definitive conclusion [20226390, 19940269, 19125208] and we agree with the conclusion of a 2008 review: “We conclude there is ample biological evidence to suggest an important role for vitamin D in brain development and function. However, direct effects of vitamin D inadequacy on cognition/behavior in human or rodent systems appear to be subtle, and in our opinion, the current experimental evidence base does not yet fully satisfy causal criteria” [18056830].

Magnesium

Magnesium is the fourth most abundant cation in the human body, and the second most abundant in intracellular fluid (after potassium). The vast majority of it (around 99%) is found within cells, so that blood levels do not necessarily provide the most sensitive indicator of body status. Around 90% of intracellular magnesium is bound to ribosomes or polynucleotides. Magnesium has a wide range of functions In membrane integrity, protein synthesis, energy metabolism, maintenance of ionic gradients, smooth muscle tone, regulation of ion channels, calcium transport and regulation of cytokine production and secretion, especially in macrophages and leukocytes. Some of these functions are due to magnesium’s function as a co-factor in enzymes, of which there are over 300, many active in brain biochemistry. Magnesium’s role in energy metabolism is particularly important, whilst other brain enzymes control neuronal and glial cell function (such as protein-kinase C, calcium/calmodulin-dependent protein kinase II and serine racemase). Magnesium is crucial for mitochondrial function and low magnesium levels have been reported in mitochondrial disorders. In many situations magnesium acts in antagonism to calcium, for example relaxing vascular smooth muscle and inhibiting calcium mediated activation of intracellular enzymes.

Of crucial importance to its brain physiology, magnesium modulates NMDA glutamatergic neurotransmitter receptors. The ion channel of the NMDA-receptor is subject to voltage-dependent regulation by

magnesium ions, with the channel being blocked at resting state by those ions. This mechanism stabilises the receptor and ensures only the proper amount of calcium influxes into the neurone. When it is not working properly, excess calcium enters, bringing about elevated levels of oxidative free radicals. Excess excitatory glutamatergic activity is one of the mechanisms through which brain damage can occur, and can follow such pathological states as brain trauma and cerebral ischaemia. This is the background to both the harm from magnesium deficiency and the potential benefit of supplementation [19944540, 19271417, 19066406, 19009818, 18402870, 18227801, 17172010, 16955724, 16358591, 15577101, 12496316, 10326720, 8747836, 5970998, 2179770].

In animal studies, magnesium supplementation has been shown to enhance memory and there is some data showing association between magnesium status and cognitive scores and academic performance in humans [20152124, 20152120, 11794635, C436].

Plasma magnesium concentration is about 40% lower than CSF magnesium, with a lower proportion of plasma magnesium being in the free ionic form that is biologically active than is CSF magnesium. Brain magnesium concentration is maintained via an active transport mechanism across the blood-brain barrier and maintains some stability in the face of varying blood levels. In any case bone serves as a substantial reservoir for storage of magnesium. But there is a point beyond which brain levels will also be affected. And conversely CSF magnesium rises by about 20-25% within several hours of parenteral supplementation. Magnesium deficiency in animal studies produces behavioural changes that are considered to be the animal equivalents of anxiety and depression. Magnesium deficiency in humans is not uncommon in clinical medicine, although very much underdiagnosed. It is a pro-inflammatory state, with increased release of inflammatory mediators such as the neuropeptide substance P. It is also a state of hyperexcitability, which can present as ventricular arrhythmia, hyperreflexia, muscle spasms and, in severe cases, recurrent epileptic fitting. On a biochemical level, it is not just NMDA receptor control that suffers, but there is a increase in excitation and decrease in inhibition across a wide range of neuromediators. This is associated with an increase in oxidative stress. Magnesium abnormalities can be associated with disturbances of calcium, potassium and phosphorus status, because magnesium is required for the proper functioning of the parathyroid, because of the metabolic interrelationships between these elements, and sometimes because the underlying clinical situation (e.g. renal disease) affects all of these ions [20971697, 20081299, 19944540, 18402870, 15637222, 12546321, 12496316, 11579331, 11153899, 10405219, 9717944, 9368238, 8264519, 1844561].

Aging is associated with decreasing intracellular magnesium within the brain, even though the plasma magnesium remains normal. There is some evidence that this is linked with age-related defects in neurotransmitter release , decreased neuronal mitochondrial efficiency and increased amyloid deposition [20413885, 20228001, 17172010, 17026853].

Apart from treatment of overt deficiency, and use of magnesium as a pharmacological agent to treat conditions such as pre-eclampsia, ventricular arrhythmia and as an acute anti-epileptic, the main clinical interest in magnesium and the brain has centred around two areas. One is in relation to depression, the other in the use of magnesium supplementation to provide some measure of neuroprotection in situations of brain trauma and ischaemia, and in premature infants.

Magnesium treatment for depression has been tried as far back as 1921 (as a sedative in agitated depression) [C498]. More than two dozen observational studies have looked at links between depression and lower magnesium status, in most cases finding one. This has included blood and CSF measurements, and links not only with the incidence or presence of depression but also with severity, with suicide attempts, the psychomotor retardation which can be a symptom of depression and with responsiveness to anti-depressants [19944540, 19780403, 19452662, 19085527, 18271494, 17845894, 16963806, 10072661, 8874848, 8369198, 8022948, 7566517, 7560548, 6743723, 6222090, 5633303, 5358528, 5103018, 5038752, 4114533, 4113542, 4112613, 2578829, 2436535, 1299790, 1184553, 591941, 573631]. Several studies have also found associations with schizophrenia [8840338, 6743723]. Despite there being as many observational studies as there are, it is remarkable how little evidence is available from RCTs. A few small trials have been reported, some uncontrolled, all on small numbers, which together do not allow of any conclusion [19271419, 15206555, 10708270, 2309035, C499, C498].

There is a sound basis for the use of magnesium supplementation as secondary prevention against brain damage in neurotrauma and ischaemia, stemming from research into the biochemical background, animal experimentation and some human observational studies. For example, there is good evidence of magnesium depletion (including of free ionised magnesium) in animal brain and human blood after brain injury, and magnesium supplementation reduces the pathological and behavioural changes of such injury

in animals [20938394, 20129501, 19780402 , 19215660, 18639191, 18557131, 17711396, 10674758, 2179770]. Unfortunately clinical trials have failed to confirm the utility of such supplementation in human brain injury, as outlined by a Cochrane meta-analysis published in 2008 [18843689, 17166799, 16580444, C500]. Various reasons have been advanced for this failure, including insufficient supplement crossing the blood-brain barrier, necessity to treat within a narrow window of time and potential for magnesium to be harmful if not given at the right time and dose [19780402, 17998974]. In a single RCT on 350 patients undergoing cardiopulmonary bypass surgery, those who received IV magnesium during the procedure experienced significantly less short term post-operative neurological deficit (short-term memory and reemergence of primitive reflexes) than those on placebo, although there were no longer-term differences [16580444]. It is hard to imagine why this trial has not been followed up in the published literature.

A somewhat different situation exists with regard to stroke. There is observational and animal evidence that magnesium can limit damage when given early on. But in this case, even though clinical trials have not been consistent in their outcomes (and similar reasons have been advanced for this `failure' as for trauma), the most recent data and meta-analysis have shown that there is an effect in the sub-category of aneurysmal subarachnoid haemorrhage. That meta-analysis was published in 2010 and included six randomised, controlled trials on 699 patients [18054611, 16427437, 16164489, 15790946, 11883835, C502]. Magnesium infusion reduced the risk of poor outcome by nearly 40% (RR=0.62, 95% CI:0.46-0.83) and delayed cerebral ischaemia by a quarter (RR=0.73, 95% CI: 0.53-1.00) [2033471].

The third clinical situation is in premature neonates, in which magnesium infusion given just before the expected birth has reduced neurological damage in the neonate in some but not all trials [19349375, 18337147, 18166581, 17169012, 14645308]. (At the same time, high doses of magnesium given to women to try to prevent the premature labour from occurring have been associated with higher levels of neurological damage in the infant [12519550]). A Cochrane meta-analysis updated in 2009 included five trials involving 6,145 babies and showed that antenatal magnesium for women at risk of preterm birth reduced the risk of cerebral palsy in the infant by a third (RR=0.68, 95% CI: 0.54-0.87) and the risk of substantial gross motor dysfunction by 40% (RR=0.61, 95% CI: 0.44-0.85) [19160238].

There has also been some speculation that magnesium deficiency may be a factor in migraine headaches, with a few small trials having shown benefit from supplements [19271946, 18705538, 11918431, 8747836]. There has been some speculation as to whether magnesium is involved in restless leg syndrome [18925578]. A number of trials have used magnesium (together with vitamin B_6) in the treatment of autism, not all controlled, most small and with inconsistent results [16846101, 16846100, 9261669, 7124567, 7010662, 6765503, 6397868, 3886023, 3170459, 3083877, 2599266, 8567594, 754238]. A Cochrane meta-analysis from 2005 found only three RCTs on 33 subjects to include, and could therefore not reach any conclusion regarding efficacy [16235322]. A handful of trials have been conducted on the use of magnesium to relieve psychological symptoms of premenstrual syndrome. Although they generally had positive outcomes, these were small sample sizes, [18582525, 17177579, 16197921, 10746516, 9861593, 2067759, 1860787].

Copper

Copper is present in small quantities within the brain and is required for normal brain function - a discovery made in 1931 in Australia when sheep feeding on copper deficient pasture developed ataxia. Copper's role in the brain has some similarities to that of magnesium. It is a cation extensively involved as an enzymic co-factor and required for antioxidant activity (e.g. CuZn superoxide dismutase) and energy metabolism within mitochondria (e.g. cytochrome c oxidase, the terminal oxidase in the electron transport chain). It also has something in common with iron, in that it is a potentially potent pro-oxidant metal, which the brain must keep in tight control in order to avoid cellular damage. In humans, adult brain concentrations of copper in the brain are achieved by the age of around 11 years, with highest concentrations being in the substantia nigra, locus ceruleus, cerebellar cortex, pallidum and putamen.

In humans, Menke's disease, a genetic defect in copper metabolism, features neurodegeneration in the cerebrum and cerebellum and dementia. On the other hand the toxic potential of copper excess is illustrated by the symptoms of Wilson's disease, which include behaviour, cognitive and movement deficits. Clearly a careful balance in copper levels within the brain is required for normal function and there are specific mechanisms for maintaining this. For example, a number of proteins `chaperone' and bind copper as it moves between the various compartments within the nervous system - what has been referred to as "copper trafficking" [20150596, 20071223, 19968254, 19356314, 11881839, C220]. There is some evidence that copper acts as a modulator of neuronal transmission, involving the NMDA receptor [16603790].

Copper in the blood is mostly (85-95%) bound to ceruloplasmin. It is the free form of copper which, like iron, has toxic potential because it is a transition metal, and it is this free form which causes the pathology in Wilson's disease. This may also be the case in several neurological conditions apart from Wilson's disease, including familial amyotrophic lateral sclerosis and Alzheimer's disease [20150596, C220]. In several observational cross-sectional studies, free (but not bound) serum copper levels were inversely associated with Mini-Mental State Examination and attention-related neuropsychological test scores in normal women, and with cognitive decline in Alzheimer's patients [20097602, 19968254, 17462944, 16155346]. In a prospective study, of 3,718 subjects aged ≥65 years, in the sub-set who had high saturated and trans fat dietary intakes the addition of high copper intake was associated with substantially faster rate of cognitive decline, equivalent to an additional 19 years over the 6 years of the study (highest vs lowest quintile of copper intake) [16908733]. Potential for excess copper arises, amongst other things, from the widespread use of copper water piping and because such inorganic copper is handled differently than organic copper [20071223, 20150596].

When it comes to clinical trial evidence, there are only two RCTs, one in which copper was given as part of a multi-nutrient supplement to 2,166 non-cognitively impaired elderly for a mean of just under 7 years, and one in which it was given on its own to 68 mild Alzheimer's patients for 12 months. In neither did it have any cognitive impact [18587525, 15534261].

Sodium and potassium

Sodium is a fundamental ion in the maintenance of the resting potential (at around -70 mV) and transmission of the impulse along nerve cell membranes. As such it is entirely central to brain activity and hence to cognition. Pumping sodium across the cell membrane is one of the major energy consuming processes of the brain, and new three dimensional MRI techniques that map subtle alterations in the distribution of sodium in the brain have been used to assess brain injury. In addition, sodium voltage-dependent channels play a part in the longer term functional structure of the brain, for example in differentiation of oligodendrocytes, the myelination and arborisation of axons etc. Moreover, the brain appears to have its own renin-angiotensin homoeostatic system with effects on neuronal regeneration after injury and the inhibition of pathological growth. Both hyponatraemia and hypernatraemia are potentially fatal conditions which include central nervous system symptoms such as impaired cognition and confusion.

However, this section of the review is short, because, except where illness disrupts it, the body's homoeostatic mechanisms for maintaining sodium and osmolality balance are elaborate and finely tuned. Therefore, under physiological conditions, there is no evidence of a practical connection between dietary sodium intake and cognition [20610972, 17118217, 17072104, 16555051, 8923799, 1375602].

Potassium is the other major cation involved in the resting potential, being the intra-cellular component. In terms of cognition, there are a number of similarities with sodium. For example, there are potassium voltage-gated channels which, like sodium channels, play an important role not just in relation to cell excitability but also more widely in longer term brain structure, hence influencing cognition and behaviour. As with sodium, potentially fatal conditions that have cognitive symptoms arise when potassium status becomes seriously disturbed (hypo- and hyperkalaemia), but there is no practical connection between dietary potassium and cognition. Some have postulated that impaired function and balance between the various ion channels may be part of the process of cognitive aging, and on that basis drugs that affect potassium channels have been suggested as potential therapies for neurodegenerative pathology such as dementia. Human experimental evidence to support this idea is, however, lacking [18459047, 15649351, 14977399, 12675669, 10213799, 4928336].

(This is leaving aside the impact of long term dietary sodium and potassium intake on blood pressure and cerebrovascular disease, such as the contribution of excess dietary sodium to hypertension in sodium-sensitive individuals, all of which is outside the scope of this review).

Vitamin K

Vitamin K, in its plant form (phylloquinone, vitamin K_1 and bacterial forms (menaquinones, vitamin K_2), is a fat-soluble vitamin whose role in bone metabolism and clotting is well established. Not so well defined is the undoubted role that it has in the nervous system. Converted to vitamin K_2 in the brain,

animal studies show that it is important in early CNS development. Animal studies have revealed that vitamin K-dependent carboxylase is highly expressed in the nervous system during early embryonic stages and that another vitamin K-dependent growth factor (Gas6) plays a part as well. In addition, vitamin K influences the brain sulfatide concentration, which is part of myelin, and the activity and synthesis of an important enzyme involved in synthesis of brain sphingolipids. In rats, vitamin K deficiency decreases sphingolipid concentrations, resulting in changes in behaviour, but not short-term memory. Vitamin K also has some antioxidant and anti-inflammatory effects in the brain [20092997, 18841274, 12843286, 10518409, 8513553, 2363732, C143]. It has been suggested that vitamin K deficiency is involved in cognitive aging and Alzheimer's disease [11461163, 10518409]. There are no relevant direct clinical trials, but an observation made as a side-light to an RCT of vitamin K given for 3 years to improve bone density found no significant differences in three cognitive tests between supplemented and placebo groups [C143].

Iodine

The requirement for adequate iodine status for normal brain development during foetal life and early childhood is probably the single most clear cut relationship between any one nutrient and cognition.

Around 70-80% of the body's iodine is found in the thyroid gland, where it is converted by a series of synthetic steps into the bioactive forms of thyroxine (T4) and triiodothyronin (T3). It is these thyroid hormones, required throughout the body for normal cell metabolism, that cause brain deficits in cases of iodine deficiency. Thyroid hormones have a role in various processes such as neurogenesis, neuronal migration, axon and dendrite formation, myelination, synaptogenesis and neurotransmission.

When the thyroid gland has insufficient iodine for its needs, it responds by reducing the synthesis of T4 in favour of T3, since the latter requires less iodine in its manufacture. This occurs even before levels of TSH begin to rise. This relative lack of T4, even in the face of `normal' TSH levels, can cause neurocognitive deficits, particularly in the developing foetus during the time it is entirely dependent on maternal T4. That is during the first 24 weeks or so of pregnancy. T4 exerts its effect in the foetal brain by being converted locally there to T3 and then binding to T3 brain receptors. These in turn regulate the expression of specific genes in different brain regions following a precise development schedule. Since these nuclear T3 receptors are present in the human brain from ten weeks gestational age, and yet the onset of fetal thyroid function is not until 24 weeks, the dependency of the foetus on maternal T4 during this time is obvious. Indeed maternal T4 still makes up between 20-50% of cord T4. All in all, this means that pregnancy brings about an increase in maternal iodine requirement of around 50% over non-pregnant levels. Thereafter the need for adequate thyroid hormone continues post-natally and for some time. After all, the brain must grow a great deal after birth, since it is only one third of its adult size at birth [20402611, 20172468, 16112266, C508, C218]!

Animal studies have shown that the impact of thyroid hormone deficiency depends on the timing. During the first and second trimesters the most obvious adverse effects are on visual attention and processing and fine motor skills, during the second and third trimesters on gross motor skills, memory and motor function, postnatally in language and verbal development, attention and memory skills. More severe lack results in lower brain weight, but greater density because of failed arborisation of axons and dendrites and retarded myelination. This occurs in the cerebrum, but especially in the cerebellum.

In humans, iodine deficiency reflects in many of these domains. The most severe deficiency state results in `cretinism' and may include mental retardation , deaf-mutism and spasticity, not easily reversible even if iodine status is later repaired. In less severe deficiencies, cognitive deficits may be seen from the second year of life and include subtle neurological changes, impaired psychomotor, learning and academic performance, and in IQ. Two meta-analyses have attempted to estimate the size of this IQ deficit in iodine deficient vs replete children. Although in both cases the methodology of the studies was a rather imperfect base from which to make an estimate of any precision, in the first case the difference reported was 13.5 IQ points [C520]. In the second case, the reviewers collated thirty seven studies from China on 12,291 children, the majority in which comparisons had been based on the area where the child lived (e.g. iodine replete vs deficient, supplemented vs non-supplemented), rather than comparing the iodine status of individual subjects. The intelligence differences reported were in the region of between 5 and 12 IQ points, with the upper end of the scale being seen in those exposed to high risk of severe iodine deficiency [15734706].

In adults, iodine deficiency is likely to manifest as hypothyroidism and in the elderly, paradoxically, sub-clinical hyperthyroidism, both of which can present with mental sluggishness [20402611, 20172468, C508].

What is most worrying from an Australian perspective is the evidence that even moderate thyroid hormone deficiency (and thus moderate iodine deficiency) during the vulnerable period of pregnancy and early childhood can result in cognitive deficit [20172468, 16396874, 19088150, 14519803]. Such modest deficiency may not even be clinical apparent and hence go uncorrected. For example, in an American study, researchers tested the 7-9 year old children of women whose only suggestion of what was in essence subclinical and undiagnosed hypothyroidism during that child's pregnancy was that blood collected from the mother at the time for the study (but not used clinically at that time) showed a free T4 below the 10th percentile at 12 week gestation. These offspring had an IQ deficit of 4 points compared with children of mothers with normal T4 during the pregnancy [10451459]. A similar result was seen at 10 months post-partum follow up in Dutch children [10396355]. This is worrying because moderate iodine deficiency is by no means uncommon, in developed countries.

The iodine content of foods varies with geographical region, depending on the content of the soils in those regions, but there are many regions where it is marginal. Moreover, although the absorption of iodine in itself is high, many plant foods contain goitrogens that reduce the bioavailability. The most reliable source is seafood, since marine plants and animals concentrate iodine from seawater [19968908, 16087997].

Globally, it remains a huge public health problem, with something like 2 billion people estimated by some experts to have inadequate iodine nutrition [20172468, 19968908]. The situation in Australia is more nuanced. The long history of iodised salt in this country led to something of a sense of complacency about the level of iodine insufficiency in the population. Yet over the last decade, studies have shown that significant proportions of the Australian population, particularly pregnant women, appear to have sub-optimal iodine status, as judged for example by TSH readings, thyroid size or urine iodine excretion [20402611]. In the Australian National Iodine Nutrition Study conducted in 2003-4, between 48% and 73% of children (n=1,709, average age 9 years) had mild iodine deficiency (based on the WHO criterion for normal status being urine iodine excretion ≥ 100 µg/L) with between 4 and 18% being moderate to severely deficient (the range of values is because figures varied quite sharply dependent on which state they lived in) [16489900]. In a modest sample of adults from the Riverina, around a half had mild and a fifth moderate to severe deficiency [18318853]. A study published in 2010 found that, amongst Australian pregnant women, 46% had mild and 15% severe deficiency [20080029]. Similar results were reported in a new study from the ACT [C521]. This `relapse' in the prevalence of iodine deficiency over the last 10 years is believed to be due to a combination of the success of public health messages about the need to reduce voluntary salt intake, less use of iodised salt by food manufacturers and switch from iodine to chlorine based cleansers in the dairy industry [16489900, 11708309]. This is likely to improve once again with the recent mandatory fortification of bread with iodine. Nevertheless, as of now iodine deficiency remains the most common cause of preventable brain damage in the newborn [19088150, 10721937].

A number of trials of iodine supplementation as primary prevention against cognitive damage have been carried out in high risk children in developing world countries, such as New Guinea, Malawi and Bangladesh. Results have been mixed, some showing improved cognitive outcomes, others not [20172468] (individual trial references: [19726593, 11208941, 11063446, 6278919, 91886, C507, C506]). In the context of the mild deficiency risk typical of Western countries, trials of supplementing pregnant women with iodine have generally produced a thyroid hormone response, but cognitive outcome in the offspring has not often been reported [19460960]. One recent study that did do so was from Spain, comparing cognitive outcomes in the children of 133 women given iodine (300 µg/day) during pregnancy (starting during the first trimester) with children from 61 women who did not receive it (but this was not a randomised allocation, hence this is an observational study). When tested at somewhere between 3 and 18 months of age, the children of supplemented mothers had higher psychomotor and behaviour rating scores than the control children [19567536]. In another Spanish study, cognitive testing was conducted at 18 months of age in children from pregnancies where the mothers were either of normal T4 status and supplemented from the 4-6 weeks pregnancy, or successfully treated for mild hypothyroxinaemia with iodine supplementation some time within the first trimester, or T4 deficient at delivery but supplemented to the end of lactation. The children of the first group had better developmental and socialization quotients, gross and fine motor coordination than the other two groups, and were the only group to have no delayed neurobehavioral performance [19348584].

A far more powerful design to address the challenge of undetected mild iodine deficiency in children was employed by a recent New Zealand trial in an older age group, in which 184 10-13 year olds were randomised to receive either placebo or iodine (150 µg/day) for 28 weeks. None had a diagnosed thyroid

problem, yet their average baseline iodine status was not too dissimilar to that of the Australian children in the National Iodine Nutrition Study mentioned in the preceding paragraph (though somewhat worse, however it is hard to be certain, since the results were reported in a slightly different way to the Australian study). The cognitive effect of this iodine treatment for just over half a year was significant improvement (compared to placebo) in 2 of the 4 cognitive subtests, and overall improvement in cognitive score of 0.19 SDs (95% CI: 0.04-0.34, p=0.011) 19726593. This is a sobering reminder that there is an undiagnosed and untreated level of iodine deficiency sufficient to affect cognitive performance existing within developed, Western countries such as our own. One can only trust that the recent change in bread fortification policy in Australia will improve this situation. Nevertheless, health professionals should remain vigilant, particularly amongst those who do not consume much commercial bread , iodised salt or seafood.

Trace elements

A number of nutrients can be grouped together not only by their chemical properties, (for example their position in the periodic table and their range of valence states), but also by the fact that, whilst they are naturally present in food and appear to be essential or conditionally essential in human (which is why we consider them nutrients), they are also potentially harmful. Many of them are commonly employed in industrial processes, and a lot of what we know about some of these trace elements in human health comes from the study of them as environmental and industrial toxins. This also applies to their impact on the brain.

Examples include manganese, vanadium, boron, tin, chromium, silicon and fluorine. The evidence for their essentiality is not as strong for some as for others. Other trace elements (such as mercury and lead) are heavy metals which do not enjoy the status of nutrients at all, and hence are not topics in this review.

The most interesting of these from a cognitive perspective is **manganese**. It is definitely an essential nutrient, found in all tissues, and required as a co-factor for a wide variety of enzymes (such as arginase, glutamine synthetase and phosphoenolpyruvate decarboxylase) involved in amino acid, lipid and carbohydrate metabolism. It is also a part of the antioxidant manganese superoxide dismutase in mitochondria, and as such is absolutely essential to life, allowing energy production to proceed without poisoning the cell with free radicals. Manganese plays a role in immune function, regulation of blood glucose, reproduction, digestion, bone growth, and together with vitamin K in haemostasis.

Manganese readily crosses the blood-brain barrier by mechanisms that may involve the iron carrier protein transferrin. It is preferentially accumulated in the dopaminergic regions of the brain. It may have a role in signal transduction pathways 19106442, 17084903, 16099026, 12505649, 11328670, 8384367.

Under normal circumstances, the body maintains fairly tight control over manganese input and excretion, so that, outside of the world of parenteral nutrition or experimental feeding labs, manganese deficiency is not a known condition and toxicity rare. However, manganese toxicity is much better established as the consequence of environmental/industrial exposure to inorganic manganese, absorbed by lung or by mouth. The neurological damage may present as a syndrome known as “manganism”. This is a progressive condition with symptoms that include dulled emotions, disturbed gait, fine tremor, and psychiatric disturbance. That these symptoms are reminiscent of Parkinson’s disease has not gone unnoticed and led to speculation that the neuropathology of manganese toxicity involves dopamine in some way, for example through excess dopamine oxidation. There is some evidence that manganese exposure during pregnancy is associated with worse fine-motor development in the infant at 6 months of age 19106442, 17084903, 16099026, 12505649, C510, C509. However, since manganese toxicity is not a nutritional condition, further discussion is outside the scope of this review.

Vanadium has a similar profile, albeit the components are much less well defined than for manganese. That is to say, it is a dietary nutrient in small quantities, with some essential functions (such as in glucose control), but with no natural deficiency state known, in contrast to which there are adverse effects from industrial/environmental poisoning. It has been speculated that abnormalities in vanadium status could be associated with the pathogenesis of certain neurological disorders. For example, an observational study of vanadium-exposed adults reported significant correlations between vanadium levels and cognitive deficits, particularly visuospatial abilities and attention. In *in vitro* experimentation, vanadium can inhibit ATPases in the parietal lobe tissues, but the precise mechanism of any vanadium neurotoxicity is unknown. On the other hand, animal experiments have shown that vanadium can be used to promote neurogenesis after

cerebral ischaemia 18311061 , 15093669. 11996408, 8013740, 6312232.

Even less can be said about the cognitive effects of the trace elements **nickel**, **tin**, **fluoride** and **cobalt**. They can each adversely affect the brain in certain circumstances (e.g. cobalt in epilepsy, cerebral oedema and neurodegeneration with nickel, intramyelin oedema and neuronal necrosis with tin) 10382559, 8029705, 3010678, 3291572. But none of this is of much relevance to nutrition and cognition.

Boron is an element whose essentiality is still under investigation, however it is believed to have an influence on physicochemical characteristics of nerve cell membranes. In animal studies, boron deprivation affects behaviour. Several small human experimental feeding trials demonstrated changes in cognitive testing in regard to dexterity and coordination, attention, perception and memory. Boron deprivation led to increase in low frequency and decrease in high frequency activity in the EEG. At the same time, boron can also be neurotoxic in overdose 18366532, 16910176, 14039168, 12705642, 10050927, 10050926, 7889884, 7889870, 1786007, C512, C261, C205.

Chromium is another compound that can be found in several valency states, most commonly 3+ and 6+. Chromium(III) plays a physiological role in insulin function and macronutrient metabolism, whereas chromium(VI) is more in use in industry and seems the more likely to do oxidative damage, including in the central nervous system. Chromium is found in the healthy human brain, as well as having been reported in abnormal deposits in neuropathological states such as brain tumour 20547405, 19167472, 18547707, 17141818, 12324196, 3958742, 1122375.

Chromium picolinate is a supplementary form of chromium that is commonly sold in health food stores. It has been proposed as a means to improve glucose control, including in the brain and indeed there is some evidence that it has activity within the CNS (although this is possibly from the picolinate, rather than the chromium) 8849977, 7838011. A single small RCT found subtle cognitive enhancements in 26 elderly subjects given chromium picolinate for 12 weeks 20423560.

Macronutrient balance

A number of studies and reviews have addressed the question of macronutrient balance in relation to cognition, both observational and through feeding trials. These studies are not distinguishable in any meaningful way from studies on the individual macronutrients, since changing one must inevitably lead to change in at least one other for a given energy content. So, for example, it is hard to know what practical conclusion to draw from a study such as the one on middle aged adults from the NHANES III national dietary survey, that found that, holding the CHO percentage of energy intake constant, there was a reduced risk of poor performance in a cognitive test for increasing% of energy from PUFA or total fat 17176641. Was this due to changes in protein intake or fat intake? One can only speculate.

In practice, a review of feeding studies on macronutrient manipulation and cognitive outcome in young adults found that most of the thirty one studies included involved glucose as the primary change made, and in only a few was the primary change complex carbohydrate, protein or fat 17629947. The cognitive effects of such macronutrient alterations may depend on the time of day when they are given, gender and individual susceptibility. Given the diversity of macronutrient composition in the various trials that have been conducted, there are substantial methodological limitations in applying the results of those trials to the topic of this review 11054612, 6764932.

Carbohydrate

Given that the principle end product of carbohydrate (CHO) within the brain is glucose, its main energy source, it is entirely obvious that carbohydrate has an immediate and central influence on brain function. In fact, as has been mentioned before, the brain is a large consumer of the body's energy supply. Since relatively little of this is used for maintenance, and most for local neural activity, the brain must exert a very fine-grained balance in its energy supplies. Studies in rodents suggest that action potentials and postsynaptic effects of glutamate consume the lion's share of the energy budget (around a half and a third respectively), resting potential only around 13%, and glutamate recycling only 3%. The astrocytes have an important role to play in storing energy and may release lactate for anaerobic when required (for example, to meet short term high processing needs in the retina) 15145548, 11598490, 11086186.

This is the setting for the utilisation of brain glucose. What needs to be summarised in this section of the

chapter is what the evidence base shows about how cognition is affected by dietary carbohydrate intake, including glucose, and how this might be affected by the form of CHO (e.g. the glycaemic load of the meal). The main focus has been on glucose, which topic can be looked at in terms of the effect of normal levels, glucose supplementation, hypoglycaemia, and the sort of fluctuations likely to be seen in poorly controlled diabetes.

There are several complicating factors when looking at this research. Dietary CHO intake is so inextricably tied up with intake of other macronutrients (protein, fat) within the overall energy budget that it is impossible to meaningfully separate in observational studies. Even in the laboratory, any manipulation of blood glucose levels will result in an insulin response which, as discussed in the chapter on protein, will in turn affect the status of other macronutrients. Once again, it is not easy to know which of these is actually impacting cognition. Indeed, much of the literature on CHO and mood is based on just that interaction, i.e. that CHO intake affects tryptophan metabolism, thereby influencing brain serotonin status [C196].

The effect of glucose on cognition has been researched in some detail, involving animal and many human laboratory studies, looking at impacts on attention, learning, memory, decision making and mood in subjects across a wide age range, and including patients with diabetes and Alzheimer's Disease. That literature has been subject to a good number of comprehensive reviews, such as the one commissioned by NASA and published in 2007 which referenced over 90 studies [C193]. It would useful to summarise the findings of that review as follows:

The available evidence supports the view that "cognitively demanding" situations deplete the brain of glucose, that those with higher levels of blood glucose perform cognitive tasks more efficiently, and that individuals' good glucose tolerance is associated with better cognitive functioning. The enhancing effects of glucose on performance and memory (e.g. on declarative memory, better retention, less forgetting) have been reported well within normal blood glucose levels. Cognitive function is correlated with glucose regulation and hypoglycaemia can disrupt cognitive functioning. This can involve both executive and non-executive functions across a wide range (including declarative memory, spatial memory, decision-making and reaction time, fine motor skill, selective and divided attention, verbal fluency, visual and auditory processing).

There is a significant variation in the extent to which individuals cope cognitively with variations in blood glucose, even within the `normal range'.

In animals, glucose administration has the potential to reverse age-related cognitive decline, so that, for example, aged mice perform as well as young mice in maze tests after glucose administration. There is some evidence for this in humans [C193].

It should be pointed out that the large majority of the studies in this area looked at short term cognitive outcomes from short term feeding of pure glucose, a situation that bears little relationship to real life dietary intake [19278571, 11502223]. When a longer term perspective was taken in a recent 6 month RCT, comparing the cognitive outcome in middle aged adults randomly assigned to either high or low glycaemic load weight reduction diet, there was no impact on cognition with either diet [19576915].

There is a significant literature on the relationship between cognition and CHO as a broader nutritional category. The conclusions in any case were rather similar to those on glucose. This literature includes associative data in relation to conditions such as idiopathic depression, season affective disorder, premenstrual syndrome, and experimental feeding trials. The findings have been various effects on mood, generally in the direction of greater calmness as well as sleepiness. There is also a body of work on the `other side of the coin', i.e. how mood can affect dietary intake, for example in relation to CHO craving and whether sweetness can be addictive (generally the evidence suggests not in the classical sense of the word) [C196, C188].

There has been one formal meta-analysis on the effect of sugar on behaviour or cognition in children. Sixteen studies (containing 23 data sets) were included, with the conclusion that there was no significant impact [7474248]. A protocol for carrying out a Cochrane review on CHO trials to improve cognition in elderly subjects was published in 2008, but the actual meta-analysis does not seem to have followed as yet [C159].

There is no doubt that chronic diabetes (and indeed metabolic syndrome) adversely affects brain health,

producing changes in areas such as the hippocampus that look somewhat like accelerated cognitive aging. It remains to be established to what extent this is due to direct effect of poor control of glucose delivery, accumulation of episodes of hypoglycaemia, secondary effects from insulin imbalance or indirect consequences of vascular pathology [19022375, 19026680, 18848880, 18673200, 18230958, 17716298, 17545744, 16246040, 16236383, 16050942, 12166601].
As mentioned earlier in this chapter, chromium, which acts to enhance glucose tolerance in certain circumstances, had a modest cognitive benefit in one small RCT [20423560].

Breakfast

In the Western diet, the meal with the highest proportion of CHO content is breakfast, hence it is appropriate to follow on from the above section with consideration of a substantial body of research on the impact of breakfast on cognition. That research has tended to focus on children and have a public health emphasis, looking at the potential of targeted breakfast nutritional support to enhance children's academic performance, for example through school breakfast programs.

A good number of observational studies have noted the link between having a healthy breakfast, (or indeed just having breakfast) and cognitive or academic performance or mood, in children [20571500, 19634483, 19631706, 19232370, 19026092, 18948652, 18604325, 17362539, 17212843, 17078979, 12947453, 9743037, 8700448, 2289961], and in adults [12000084, 11897269, 10719585, 10367010, 2007155]. Some three dozen clinical trials on generally healthy subjects were considered for this review, a little more than a half of them were conducted on children or adolescents. Most looked at cognitive or academic test scores, nine considered mood measures.

What does the literature show? A systematic review published in 2009 included forty five studies published between 1950 and 2008 on the impact of breakfast on cognition in children and adolescents. The large majority were in children, some were trials, others observational studies, some in subjects at risk for nutritional inadequacy, others not. The authors concluded that having breakfast does have a positive outcome on cognitive performance compared with not eating it, and that this was more apparent in the at-risk children. However, they also cautioned that there was a lack of research comparing different compositions of breakfast, so that it was not possible to recommend that any one type of breakfast (whether in amount, macronutrient composition etc.) would be effective. Regarding academic performance, the evidence suggests that breakfast interventions can have positive effects, but this may be in part explained by the increased school attendance that is brought about by participating in such an intervention [19930787].

This conclusion is consistent with, though rather more qualified than, that of another review, one which focused specifically on the US school breakfast program (and which was commissioned by an anti-hunger philanthropic body). This second review was based on consideration of over 100 papers, and concluded that: "the combined and quite consistent message of this body of research is that serving breakfast to those schoolchildren who don't get it elsewhere significantly improves their cognitive or mental abilities, enabling them to be more alert, pay better attention, and to do better in terms of reading, math and other standardized test scores. Children who eat breakfast also are sick less often, have fewer problems associated with hunger, such as dizziness, lethargy, stomachaches and earaches, and do significantly better than their non-breakfasted peers in terms of cooperation, discipline and inter-personal behaviours" [C411].

However, whilst this highlighting of the broad range of health and social benefits of such a program does suggest its public health benefit, it also highlights the potential for extensive confounding in establishing any specific causal link between a nutrition input and its cognitive consequence. This, and the lack of standardisation of what nutrients we are talking about when we talk about "breakfast", means that this whole area of research has only limited applicability to our understanding of nutrition and cognition [18948650].

General nutritional supplementation

The same argument can be applied with even more force when it comes to the significant research base on the cognitive impact of giving general nutritional supplementation, or various combinations of micronutrients. There is no shortage of trials of this nature - sixty eight such studies were identified for this review. They span paediatric, adult and geriatric age groups, healthy subjects and those with medical conditions such as attention deficit disorder, mental retardation, autism, depression, cognitive decline and dementia. Some might be better addressed in the section on malnutrition, for example energy-protein-micronutrient supplementation for undernourished children in developing countries such as Indonesia,

South Africa, Jamaica or the Philippines [17016955, 12907410, 10902994, 10902993, 9250101]. But because of their polynutrient composition it is impossible to know which nutrient actually gave rise to the cognitive improvement reported. This is even harder to decipher when the subjects in the trial were healthy and not at risk of malnutrition.

In short, these studies are of more importance to public health than to cognitive science.

Four systematic reviews have looked at the question of multinutrient supplementation and cognition from different perspectives. One published in 2010 included three trials in children under 5 years (n= 1,429) and seventeen on children from 5 to 17 years (eighteen data sets, n=5,681). Based on the twelve trials in the older children that could be combined, there was no significant impact on crystallised or fluid intelligence, but there was a positive effect from four trials on academic performance (difference of 0.30 SD, 95% CI: 0.01-0.58, p =0.044) [19889823]. Another review combined results from thirteen trials using multi-micronutrient supplements on 1,451 schoolchildren and measuring the change in IQ as the outcome. For some reason the authors also included two trials on young men in prison, adding in another 276 subjects over 18 years, as well as 26 teenagers aged 13-17 years. Although five of these studies failed to show any statistically significant difference in IQ after supplements, the trend towards a positive result was seen in each of the trials, so that the combined impact was a difference of 3.2 IQ points (p=0.0001). The authors felt that closer inspection of the variance data suggested that this IQ benefit was due to much larger gains in just a few children within each trial, which they presumed to be the less well nourished ones (on what basis is not clear) [10328634]. A third structured review of vitamins, minerals or fatty acid supplement trials on cognitive decline included too many that were not polynutrient in nature to make a useful contribution to this section [18721399].

A fourth review focused on trials involving complimentary feeds with paediatric development as the outcome. The authors found only three in which provision of such feeds was the sole intervention, and two in which micronutrients were added. Needless to say this was too few to provide meaningful conclusions from collating the data [18289157].

The fifth systematic review was on the elderly. It was published in 2004, and the authors located only four RCTs of multi-nutrient supplements suitable for inclusion, on 514 subjects, the latest from 2002 [15528776]. Two of these trials had reported positive cognitive outcomes [12042457, 11527656], the other two found no significant differences [11157333, 9003882]. As with review #3 above, this paper included a majority of single nutrient intervention trials and hence its conclusions do not assist us in this section. Moreover, one of those two positive studies was retracted in 2005 under controversial circumstances [15793927].

Overweight

If ever there was a relationship replete with confounding influences, it is the one between overweight and cognitive state. Mood disorders can prompt a person to overeat, and being overweight can have such strong impact on people's feelings and thinking. Cognitive traits can influence eating habits (e.g. decision making ability). Common factors can contribute to obesity and cognitive impairment, for example diabetes or metabolic syndrome through atherosclerotic cerebrovascular disease and hypertension. Complications of overweight such as sleep apnoea that can affect brain oxygenation. Studies on the cognitive effects of weight reduction diets present the difficulty of distinguishing the impact of the weight reduction on cognition from the effects of the dietary changes involved in the diet (such as reduced energy, fat or carbohydrate). In order to make any headway in this topic, we need to leave these issues aside, and focus on the simple question of whether the state of overweight, per se, affects the neurophysiology of cognition.

This approach dictates an appropriately cautious perspective on the observational evidence reporting on the link between overweight with lesser cognitive performance. Of that there is no shortage, mostly showing the association, some not. These have been conducted in children and adolescents [19766958, 19437203, 18551126, 17761359, C104], young to middle aged adults [20135940, 19425460, 19260167, 19073790, 18448310, 18276751, 17145283, 16321166, 16250089, 16231030], older subjects [20299802, 19998366, 19816410, 19108905, 19046243, 18443570, 18358569, 16420204], and those with cognitive decline and dementia [20727007, 20570405, 19168781, 18992327, 17881716]. Studies have shown an inverse relationship between BMI and prefrontal metabolic activity in healthy adults, and a link between obesity and lesser whole brain and total and focal gray matter volume and enlarged orbitofrontal white matter [18992327, 18948965, 18853335].

In animal experiments, obesity is associated with changes to myelin, increased amyloid deposition and oxidative stress, which looks rather like the changes seen in accelerated cognitive aging [18992327].

Why might this be? One reason could be the adverse effect of the imbalanced diet that caused the obesity in the first place (e.g. high fat). It could be related to the insulin resistance that forms part of the metabolic syndrome route to overweight [20633104, 20444434, 19712582, 17545744]. There has been some interest in the CNS handling of insulin as a possible area of therapeutic targeting, talking about “central nervous insulin resistance” and the potential ways one might be able to treat it in the future [19705099, 16444902, 12701881].

Another reason might be the impact within the brain of the systemic inflammatory state that characterises obesity. There is certainly some evidence for this. For example, in observational studies the link between overweight or metabolic syndrome and cognitive decline is more pronounced in those with elevated inflammatory markers [18347963, 17430234]. In animal experiments, maternal obesity is associated with higher levels of brain inflammation in the offspring [20124437]. It might be related to specific hormones associated with adipose tissue, weight regulation and obesity, the so-called adipokines [18992327, 18358569].

One of those hormones is leptin which, apart from any role in regulating appetite, has a range of effects relevant to cognition. These include stimulation of nerve growth, modulation of the NMDA receptor in the hippocampus and potassium channels in several brain regions. There are leptin receptors in the limbic system. Altogether, the stage is set whereby leptin can potentially influencing motivation, learning, memory and other cognitive functions [20399755, 19130879, 18992327, 18675793, 18024215, 11734601]. Interestingly in a case report of a child with congenital leptin deficiency, replacement of the leptin resulted in cognitive and neurodevelopmental improvement [18769731].

Finally there is the question of cognitive impact of weight reducing diets. As mentioned above, this is something which is hard to separate from the nutritional changes that are part of such diets. But there certainly has been concern that severe or nutritionally imbalanced diets, or some neuropsychological impact of highly restrained eating in itself, could adversely affect brain function. One area of focus has been with whether dieting, or weight loss, could cause depression, clearly a condition closely linked with overweight in any case [19213197, 8300977, 4606433, 3312589]. And of course there is the powerful confounding factor of emotional changes that would follow upon the psychological stress of the dieting process, and the rewards of successfully losing weight.

There has been some observational [9794013, 8587997, 8190760, 8467272] and a little trial evidence [9023595] of cognitive changes in subjects on weight reducing diets, including on ketogenic diet [8589783]. A specific issue has been whether changing the macronutrient composition of the diet could affect the status of tryptophan and hence serotonin, and this has been seen in low-calorie dieting [8931161, 3432460, 2284387]. Based on the neurophysiology discussed in the previous chapter on protein, the type of diet where one might most expect to see this is those with significant change in carbohydrate:protein ratio. However such trials as have been reported along those lines have had mixed results in regard to mood and cognition, insufficient to reach any clear conclusion [19901139, 18804129, 17823420].

Water

Water is the most abundant of all substances in the body ingested by mouth. Making up between a quarter and half of the body weight, it literally fills not only most cells and the spaces between them, but is part of the biochemical structure of some of the macromolecules that in turn create larger structures. It is, of course, a key constituent of the fluids (blood, CSF) which bring nutrients to the brain. It is only to be expected that body hydration would have some effect on cognition [9972188].

In reality this topic has been rather neglected in clinical research. Severe dehydration is a fatal condition, and passes through stages of delirium and coma prior to death, and even moderate dehydration can be associated with symptoms of irritability and confusion, suggesting involvement of the brain. But there are relatively few studies on the cognitive effects of mild degrees of water lack, degrees that one might label sub-clinical dehydration. Such observational studies and trials as we do have mostly been conducted in healthy young adults, sometimes within a military or space medicine context. Not only the cognitive measures used but the resilience of the subjects to the adverse effects may not entirely reflect how less fit, middle aged people would react. In addition a common study design involved heat and physical stress as well as water lack, which factors are likely to have influenced the results in their own right. On the

other hand, in a non-experimental situation of clinical dehydration, one is often dealing with significant electrolyte disturbances as well as the actual lack of water, for example hypernatraemia, which can confound any observations of cognitive deficit thought to be due to water deficiency itself. (Electrolyte and acid-base pathophysiology is the province of intensive care medicine, not this review!) [17921473, 17921465, 17921464, 17063927].

The data we do have shows lower cognitive test scores in dehydrated adults. Individual test subjects who have been put through dehydration tests of up to 37 hours have reported feeling headaches, and less alertness and ability to concentrate. Other parameters shown in at least one study to be affected by dehydration are: psychomotor performance, arithmetic efficiency, attention, choice reaction time, short- and long-term memory, perceived discrimination, perception of fatigue, target shooting and visual-motor tracking. The critical point beyond which these effects are detectable seems to be around 2% water loss, which in conventional clinical terms is very mild dehydration, since mild dehydration normally begins at around 3% of body weight [17063927]. Some studies have seen it at even lesser degrees and some not until slightly higher. Individuals who are highly fit (e.g. athletes, military recruits in training) may not be as susceptible [19831106, 19501780, 18166204, 15845879, 15182398, 11812391, 7417123, 5027711, 3743537, 3355239]. Some cognitive changes have also been seen in dehydration in the elderly [15210289] and in children [16303708]. On the other hand, a small observational study of elderly patients undergoing bowel preparation did not find any cognitive impact of their average water loss of 2%, compared with controls [18292441].

There is little data on the other side of this equation, i.e. whether giving water to healthy subjects who have no apparent evidence of being dehydrated improves cognition. This was done in one randomised controlled trial on 58 primary school children (7-9 years old). Those subjects given additional water did significantly better than those not given it on tests of visual attention tasks ($p<0.02$) [19501780].

Various mechanisms have been proposed to explain how dehydration might affect cognition. These include release of stress hormones upon activation of the hypothalamic-pituitary-adrenocortical axis, neuromodulator effects of vasopressin (the primary function of which is to stimulate thirst), and changes to both excitatory (glutamate) and inhibitory (GABA) neurotransmitters [17063927].

Other nutrients and nutritional factors

Mitochondrial co-factors

Acetyl-L-carnitine and **α-lipoic acid** are examples of mitochondrial co-factors, i.e. compounds that have an involvement in mitochondrial metabolism. Neither is a recognised nutrient as such, with the former being a metabolite of the non-essential amino acid carnitine, and the latter widely found in food but in a covalently bound form that is not easily absorbed. It is synthesised within the body from fatty acids.

Both have important functions in nutrient metabolism. L-carnitine is required for the transport of LCPUFA across the inner mitochondrial membrane to their site of oxidation and the production of energy in the form of ATP. It appears to be capable of stabilising cholinergic neurotransmission, influences neuronal apoptosis and has neurotropic actions. Similarly α-lipoic acid has antioxidant and anti-inflammatory actions within the CNS and is unusual in that it is both fat and water soluble. Hence it readily passes through the blood-brain barrier.

On this basis, both compounds have been considered as potential supplements to help counter the process of mitochondrial deterioration and associated oxidative damage that is thought to underlie cognitive decline with age, as well as help protect against diabetic neuropathy. In some animal experiments, such supplements have indeed shown signs of doing so [20857196, 19669875, 19185780, 18846423, 18787974, 18655815, 18373733, 17622567, 17605107. 15591008, 8389716, C128, C122].

There is at least one RCT, in 66 easily-fatigued centenarians, in which carnitine supplements improved cognitive test scores and reduced fatigue [18065594]. A Cochrane meta-analysis on carnitine supplementation for dementia, published in 2003, found eleven RCTs suitable for inclusion. The collated data showed improvement in clinical global impression at 12 and 24 but not 52 weeks [12804452]. There has been an open-label trial of α-lipoic acid in Alzheimer's disease [17982894]. A review of five RCTs using it for diabetic neuropathy concluded that there was evidence of benefit [17272797].

Other

Ferulic acid is a derivative of cinnamic acid and, although not generally considered a nutrient as such, is found in vegetables and fruits. It can be synthesised from phenylalanine and tryrosine. It has antioxidant and anti-inflammatory actions within the nervous system, as well as some neurotropic effects. In animal experiments it has been tested as a possible therapeutic agent for cerebral ischaemia, neurodegeneration and Alzheimer's disease. Human trials are lacking [19837139, 19051339, 19026158, 18400211, 17007737, 16634068, 16038626, 15056291, 14766058, C128].

Lecithin (or phosphatidylcholine) was mentioned in the section on choline in the earlier chapter on Other B vitamins. A Cochrane meta-analysis from 2004 identified twelve RCTs involving lecithin on 376 patients with Alzheimer's disease, Parkinsonian dementia and subjective memory problems. None reported any clear clinical benefit of lecithin for Alzheimer's disease or Parkinsonian dementia. The trial on subjective memory loss did show some benefit, but the authors of meta-analysis considered the collated data insufficient to conclude lecithin has any effectiveness for cognitive impairment [12917896]. A more recent small trial reported EEG changes in the cortex in response to stress after 42 days of lecithin supplementation, but the significance of this is not clear [18616866]. An RCT on 120 older patients with memory impairment failed to demonstrate any cognitive benefit from 12 weeks of soy-derived lecithin supplementation [11842880]. There was only minimal enhancement of the cognitive benefit of gingko when lecithin was added in another small trial of young healthy adults [17457961].

Gangliosides are glycosphingolipids, and the fact that they were named after the brain ganglia in which they were first identified is an indicator of their structural function within the brain. Sialic acid is the name for a number of monosaccharides that make up one of the components of gangliosides. They are naturally present in the food supply and rich in human milk, for example as N-acetylneuraminic acid. Formula milks, on the other hand, may not be as rich. Although they make up a small portion of the overall sphingolipid intake of the diet, they are concentrated within the central nervous system, constituting 6%-10% of the total lipid mass of the human brain. They make a substantial contribution to brain structure and function, including an especially prominent role during brain development. They are involved in neurotransmission, neuronal outgrowth, modifying synaptic connectivity, and memory formation. In terms of this review, the practical interest lies in the animal studies directed towards cognitive protection or enhancement. Although these have had mixed results, there have certainly been studies in higher animals (such as piglets) in which supplementation of sialic acid has led to enhanced synaptic connectivity and learning. There are no human clinical trials relevant to cognition (apart from a single open trial from China on 2,230 children with cerebral palsy) [19674342, 19575597, 14576748, C513].

Phytoestrogens

As mentioned earlier in this chapter (under flavonoids), there are a number of compounds that come under the category of phytoestrogens, defined as being of plant origin (e.g. soy, red clover etc.) and having the capacity to exert oestrogen-like effects at certain doses. There are three main classes: isoflavones, lignans, and coumestans.

The cognitive potential for phytoestrogens therefore takes as a starting point the established properties of oestrogen in relation to cognition. Oestrogen receptors are widely distributed within the brain, both ER-α and ER-β sub-types, predominately in the limbic system and cortex. It has been shown in animals that oestrogen has neuroprotective effects on the cholinergic neurotransmitter system, within the hippocampus and frontal cortex, and may regulate the density of dendritic spines and synapses of hippocampal pyramidal neurons. Another potentially important oestrogen effect that can influence cognition is cerebral vasodilatation, and functional imaging studies have shown this specifically in the hippocampus and cortex areas associated with learning [15226476, C516]. The therapeutic basis for use of phytoestrogens is that they will emulate those effects within the brain, and indeed there is some *in vivo* and *in vitro* evidence of just that [18818291]. (And that they will not emulate the findings of the recent Women's Health Initiative trial, which reported that women on oestrogen replacement therapy had a higher risk of cognitive decline and dementia than those on placebo [19932751]).

The human clinical trial evidence on phytoestrogens and cognition (a sub-set of the trials discussed in the earlier section on flavonoids) has produced somewhat mixed results. A total of twenty trials have been published on 1,152 subjects (15 in women only, of which 11 were on post-menopausal subjects, 2 on men only and 2 in both genders). Although two thirds had positive cognitive outcomes, in some cases this was only of minor significance, and generally the trials had very diverse methodologies, with 3 not

being controlled, formulation and dosage differing and treatment duration varying from a few days to months. Most had small subject numbers. Although no formal meta-analysis has been published, many of these trials have been included in the tabulation of two review articles (from 2007 and 2009) [17997703, C515]. It is likely that, if a thorough systematic review were to be done, the conclusion would be that the data is interesting, but far from convincing. Issues that remain to be resolved include dose, timing, whether the phytoestrogens should be specifically oestrogen receptor-β binding, and whether equols should be contained in the mix.

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Chapter P: Protein and amino acids

Executive summary

Protein has a major role to play in the brain, as a structural element, as a secondary fuel source, as a substrate for the synthesis of neurotransmitters and other neuromodulators, and as part of the control mechanisms that maintain neurotransmitter balance.

Some of this has to do with protein sufficiency within the total diet. Whilst it is difficult to separate protein deficiency from overall malnutrition and the social and economic environment in which malnutrition occurs, it is generally acknowldged that severe protein deficiency has long lasting cognitive effects. In humans this results in impaired learning, broad based cognitive, behavioural and academic deficits, more global than localised, and which can persist at least into adolescence. These adverse effects are most likely when the deficiency occurs during the vulnerable period perinatally and during the first two years of life. They are, however, subject to correction if the nutritional circumstances are corrected, particularly if repletion takes place before the vulnerable period has elapsed and especially where the socioeconomic environment has also improved.

Amino acids have more direct impacts on brain biochemistry, as they cross the blood-brain barrier by specific transport mechanisms, a separate one for each of large neutral (LNAA), basic and acidic amino acids. Because the transport mechanism for the LNAA group is nearly saturated at physiological amino acid levels, there is a competitive inhibition such that increased blood concentration of one LNAA (e.g. a branched chain amino acid) will reduce brain levels of the others (e.g. aromatic). When this is combined with a neurotransmitter synthetic pathway that is highly sensitive to precursor levels, it provides the means for dietary amino acid intake to directly influence brain neurotransmitter levels. Some amino acids are themselves neurotransmitters or exert moderation and some level of control over excitatory neurotransmission.

The link between dietary amino acid intake and cognition his been most clearly demonstrated for the aromatic amino acid tryptophan, in relation to its neurotransmitter metabolite serotonin. Various manipulations of the diet can influence serotonin levels, including the type of protein, the amount of carbohydrate (via insulin response driving protein into muscle), and of course direct tryptophan supplementation. The effect of depletion is a modest decrease in mood and increase in irritability, most likely to be seen in those with a prior disposition to depression. The opposite is seen with supplementation, plus some sedation and increased pain threshold.

The other aromatic amino acids have similar biochemical relationship to their catecholamine metabolite neurotransmitters (dopamine and noradrenaline), though in human studies the main effect seen has been reduced cognitive impairment caused by high stress situations.

Branched chain amino acids (e.g. leucine and valine) have a role as a secondary energy source for the brain, as well as helping to regulate aromatic amino acid brain levels via the competitive inhibition mentioned above.

Glutamine plays a central role because of its relationship to the main excitatory neurotransmitter glutamate. This has a key role in memory, and the body has complex mechanisms to regulate glutamate concentrations within and around the synapse, some of which involve other amino acids (e.g. BCAA).

The few randomised trials using these amino acids to affect cognition or mood in clinical situations are insufficient to allow any firm conclusions to be reached.

There is some observational evidence showing that higher consumption of meat is associated with better neurodevelopmental and cognitive outcomes, and a little RCT evidence from Kenya. However, this is insufficient to allow us to confirm a specific cognitive effect of meat distinct from its nutrient components.

The neurophysiology of amino acids needs to be considered in two broad categories. Firstly there is the role of protein as a macronutrient, and the consequences of protein deficiency. Secondly there are the specific roles of individual amino acids or groups of amino acids (e.g. branched chain, aromatic), including in relation to neurotransmitter systems.

Protein

Physiology

That protein is required for structural development in the brain is so self-evident as to barely require stating. Protein is also at the heart of learning and memory. In some cases this involves synthesis of new protein, in others changes to existing protein. For example, in a widely proposed theory of memory, short-term neuroplasticity is believed to be mediated by post-translational modification of proteins, whereas long-term memory occurs when learning-dependent new protein synthesis is targeted at the synaptic nodes recently activated by that learning, rendering the change specific and permanent [18494028, 15626492].

Yet this theory is still actively debated, and it is safe to say that any coherent, universally agreed model of how protein affects the brain remains elusive. In part this is because of the general challenge of finding a model which is representative of the real life brain environment, particularly the human brain. A good deal of research into the function of protein in the brain has been done (in animals and *in vitro*) using protein synthesis blockers, the relevance of which to normal conditions has been subject to much debate [18494028].

In tackling the issue from the perspective of protein deficiency, another problem arises - how to separate the effect of protein lack from that of energy deficit and general malnutrition. Of course this is not so difficult in the laboratory or in short-term human feeding studies. But in ‘real life’ human clinical situations, researchers have often based their conclusion on observation of people suffering from moderate to severe protein lack, and in that situation the distinction is not so neat. It is true that patients with severe malnutrition can be divided into those with marasmus, where there is a more generalised deficit of both energy and protein, and kwashiorkor, where clinical features are more typical of protein deficiency (e.g. the presence of oedema causing the characteristic protruding belly). But clinicians know these are diagnostic categories of convenience within a composite condition of protein-energy malnutrition (PEM), rather than strictly distinct conditions with sharp boundaries.

Another complexity arises because protein is an important part of the transport, storage or functional form for many other nutrients, including those with major cognitive function, such as iron, zinc and fatty acids. Hence it is entirely possible that any cognitive deficit seen in patients with protein deficiency could actually be due to a functional deficiency of those other nutrients. A good example of this is the evidence, including human studies, showing the interrelationship of protein and essential fatty acids in regard to cognitive impairment of PEM [19086537, 17284765, 7542705].

A further issue is the difficulty (particularly in observational studies) in distinguishing between the effect of the general socioeconomic and health environment in which a malnourished child grows up, and the specific effect of the nutritional deficits. Not to mention the indirect effects of malnutrition on infectious resistance, growth and other aspects of health that can themselves affect cognition. In talking about protein, one also has to consider the quality of the protein, particularly its completeness in regard to essential amino acids. Since high quality protein (e.g. meat, fish) is usually the most expensive of the macronutrients, the association between inadequate dietary protein intake and poverty is particularly close [18752473, 15383435, 8560214].

Despite all these challenges in interpreting the research, it is nevertheless generally acknowledged that PEM in its various forms is one of the three most globally prevalent nutrient deficiencies compromising children’s normal development of learning and psychomotor skills [5337244].

In terms of specific cognitive functions, the role of protein in learning and memory has already been mentioned. The exact role remains under debate because ongoing research using protein synthesis inhibitors has made it clear that memory formation does not always require new protein. Post translational modification is one piece of the puzzle, but one can also legitimately ask, considering how much protein synthesis is occurring during memory formation, what does it get used for? Possibilities include: that new protein is needed to maintain overall neuronal cell integrity, to replenish existing protein that was engaged into the plasticity mechanisms, or to support some other function (including neurotransmission) that in turn

is crucial for the memory to be laid down [18328411, 18054504].

Deficiency states

Experimental protein deprivation results in changes to the hippocampus, including the GABAnergic system, pathological enhancement of inhibition and diminished plasticity [12204193]. Prenatal protein deficiency causes structural, cognitive and behavioural deficits [17284765, 8804664, 8973843, 7722680, 7470928, 402808]. Specifically one will see lower neuronal number, reduced protein synthesis, hypomyelination, reduced brain size is reduced along with changes in structural proteins, growth factor concentrations, and neurotransmitter production At the ultrastructural level there will be reductions in synapse number and dendritic arbor complexity. Anatomically these changes tend to be global when it comes to cell proliferation and differentiation, affect the cortex in regard to synaptogenesis and the hippocampus in relation to growth factor synthesis. The cortex and hippocampus appear to be particularly vulnerable to protein-energy malnutrition (PEM) [17284765].

The cognitive and developmental deficiencies for humans that follow on a period of severe PEM are well established. They result in cognitive, behavioural and academic deficits that can persist at least into adolescence [7542705, 7542707]. These may be reflected in demonstrable MRI abnormalities [16019576]. The cognitive deficits tend to be global rather than specific. Behavioural changes include impaired social-interactivity and less affable temperament [3808797, 2731496, 19605526, 17284765, 16277829]. There is some evidence that children are most vulnerable to the longer term effects if the deficiency occurs in the first two years of life [15806897, 10828173, 7542706, C343].

Even mild to moderate malnutrition has adverse effects, though much of this has been established by reverse inference from supplementation trials. These include impact on infant motor development, cognitive scores and developmental quotient at preschool, and academic performance at school age [7542706]. Chronic PEM in the age ranges 5-7 and 8-10 years was found to have affected the ongoing development of higher cognitive processes rather than merely a generalized cognitive impairment in a small, cross-sectional observational study from India [18652660]. It affected maths and language scores in another cross-sectional study of over 3,000 children from Vietnam [11528497].

These deficits are to various extents able to be improved if the malnutrition is subsequently corrected and more likely so if this correction is started within that first two year ‘window’ (although there is evidence that the effects of malnutrition in the hippocampus and cerebellum may be harder to reverse) [16277829, 7542703, C343]. The literature on this topic is extensive, and beyond the scope of this review. However, it is also subject to ongoing debate and controversy, because such interventions as have been trialled, or improved nutritional status as has been observed, are inevitably associated with significant improvement in the environment of the child overall. That includes their physical health and the amount of support and stimulation they receive. This has made it hard to say if the observed cognitive correction has anything specifically to do with undoing the protein deficiency, or is simple the result of the better living circumstances [10828173, 10721904, 7542705].

Amino acids

Amino acids contribute to brain function in various distinct ways. Firstly, they are incorporated into whole proteins to serve the functions of proteins that have been discussed above. Secondly, they are an energy source, although the brain preferentially utilises glucose for this purpose. Thirdly, they are required for the synthesis of certain neurotransmitters and neuromodulators (e.g. tryptophan, tyrosine, histidine, phenylalanine, arginine) - see Table P1. Fourthly, they help regulate the activity of excitatory neurotransmitters such as glutamate, for example through their interaction and competition for absorption with other amino acids. The influence on neurotransmitters is particularly direct, given that, of the well over 50 compounds that exert such a function within the brain, most are peptides [17721727, 15930466,, 2878467, C248, C211].

Table P1: Amino acids and their neurotransmitter or modulator metabolites [C248]

Amino acid precursor	Neurotransmitter/ neuromodulator
Tryptophan	Serotonin Melatonin
Tyrosine Phenylalanine	Dopamine Noradrenaline Adrenaline

Histidine	Histamine
Arginine	Nitric oxide
Threonine and others	Glycine

The eight essential amino acids that cannot be readily synthesised by the body from other precursors are: phenylalanine, valine, threonine, tryptophan, isoleucine, methionine, leucine and lysine. Others such as taurine are considered semi-essential, because the body's capacity to synthesise them is limited in certain age groups or circumstances. The amino acids that are the most important from the perspective of dietary influence on cognition are the large neutral amino acids (LCNAA), which in turn can conveniently be divided into branched chain (BCAA - leucine, isoleucine and valine) and aromatic (AAA - tryptophan, phenylalanine, tryrosine) classes. The latter are directly involved in the synthesis of serotonin (tryptophan) and catecholamines (dopamine and noradrenaline). (Methionine is another LCNAA but its cognitive functions have already been discussed in the chapter on homocysteine).

To understand the role of the different types of LCNAA in relation to neurotransmission, it is necessary to discuss briefly the absorption of amino acids across the blood brain barrier.

The amino acids cross the blood brain barrier via active transport mechanisms that are separately specific for large neutral, basic and acidic amino acids. The mechanism for LCNAA is shared by the two classes of that type, namely BCAA and AAA, and is almost fully saturated at normal blood amino acid concentrations. Therefore, because of competitive inhibition for transportation into the brain, an increase in the blood concentration of one class - as may readily be brought about by a change in the diet - will result in a fall in brain concentration of the other class. Similarly, an increase in any one particular amino acid within either class will result in less absorption of other amino acids within the same class.

This is particularly relevant to neurotransmitter synthesis because firstly, neurotransmitters cannot generally be absorbed across the blood-brain barrier and must be synthesised within the brain, and secondly because those synthetic pathways are highly sensitive to the concentration of precursor amino acids. If we add into the mix a web of interconnected biochemistry linking many of the amino acids together by synthesis and interconversion, it is clear how the body could use amino acid concentrations in blood and brain as part of its complex mechanism for tightly regulating neurotransmitter concentrations within the neuronal terminal vesicle and across the synapse - clearly something at the very heart of the cognitive process. And how, in theory at least, that mechanism could be influenced by dietary protein intake [2980858, 15930466, 2878467, C283, C248, C211, C101].

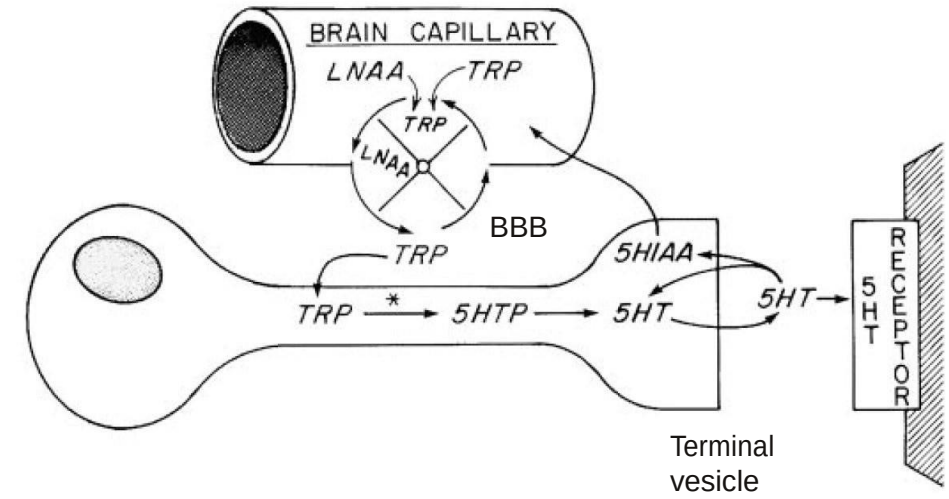
Exactly how a given diet will influence the amino acid balance in either blood or brain depends, of course, on the composition of that diet. In most dietary proteins tryptophan is one of the lesser abundant amino acids, whereas phenylalanine and tyrosine are more abundant. On the other hand, milk contains small amounts of α-lactalbumin, a protein which has a rather high tryptophan level 17476368.And it is not just the type of protein which influences brain amino acid levels, but also the balance of other macronutrients, particularly carbohydrates. Thus high carbohydrate meals will usually increase, and high protein meals (particularly up to 15 gm/day) usually decrease the proportion of tryptophan to other LCAA with similar but lesser effects on tyrosine:LCNAA ratio 12499331, C216. This is at least in part due to the effect of carbohydrate in increasing insulin release, which in turn drives BCAA into muscle 11826946. The action of insulin is also part of the reason why it is not a simple matter to predict how amino acid levels will change by simply looking at the amino acid content of the food eaten 1266783. One also has to take into account such things as the binding state of the amino acid (e.g. the amount of tryptophan bound to albumin, which in turn is affected by the fatty acid content of the blood), the blood pH and various other factors which can influence the uptake of an individual amino acid into the brain C103.

There is one more element to this relationship. This is the effect that neurotransmitters themselves have on appetite. In animals, serotonin stimulation decreases food intake, particularly for carbohydrate. So a feedback loop for macronutrient intake could be established in which increased carbohydrate increases brain serotonin which leads to suppression of carbohydrate at the next meal, and the opposite for protein. Whether this applies in any practical way in humans is yet to be established C211.

Tryptophan

The strongest evidence in humans of such a direct influence of dietary amino acid intake on neurotransmitters in the brain is for tryptophan in relation to serotonin. Serotonin is a good example of a neurotransmitter that does not cross the blood-brain barrier and hence can only be synthesised *de novo* from tryptophan within the central nervous system. Of the two forms in which tryptophan exists in the blood (bound and unbound), it is the unbound form that crosses into the central nervous system. Competitive absorption involving tryptophan and its impact on serotonin was first reported in rats nearly 40 years ago with manipulation of tryptophan status being achieved by feeding extra carbohydrate and has since been shown in animals given protein feeds which have less tryptophan relative to other LCNAA. This results in a decrease in brain serotonin, both in the short and longer term 19594222, 7840068, 3101981, 7749758, 5581909, 5120086, 5077329, C101. The mechanism is shown in Figure P1.

Figure P1: Synthesis of serotonin and its relationship to tryptophan status 15930466



LCNAA: long chain neutral amino acids, TRP: tryptophan, 5HT: serotonin (5-hydroxytryptamine),
* : rate limiting enzyme (TRP hydroxylase), BBB: blood-brain barrier

So direct is this effect that both tryptophan depletion and tryptophan exclusion have been extensively used to study the serotonergic system within the brain, in humans and in animals [19715722, C211]. The most obvious result of tryptophan depletion in humans is a modest negative effect on mood. Before describing this in more detail, it will be helpful to consider some of the background to this system in relation to the way the human brain processes emotion.

It is not easy to locate emotional response to specific anatomical structures or biochemical systems, but a great deal of research in animals and in humans (using, for example, pharmacological interventions and brain scanning tools) has gone into attempting to do just that. Affective behaviour involves integrated circuits organised across hierarchical systems at all levels - hindbrain, midbrain, and neocortex. The most prominent areas are in the prefrontal cortex, basal ganglia, thalamus, hippocampus, and amygdala. These are concerned not just with the subjective feeling, but also with the physical response, for example the hindbrain circuits that initiate somatic and visceral response to arousal. The midbrain, circuits in the limbic system and prefrontal cortex stimulate cortical arousal by activating pain or pleasure tracts involving the periventricular system and medial forebrain bundle. This involves the hypothalamus, amygdala, and hippocampus. Meanwhile the forebrain, particularly the frontal lobes, is integrating internal and external sensory input with past experience and the wider `mindset' of the individual, to formulate the person's conscious and semi-conscious response, including whether to encourage or suppress the emotional activity. The systems involved in this emotional processing use a number of neurotransmitters, within which tryptophan is certainly prominent, particularly in regard to subjective emotional perception, and probably the one for which we have the most extensive evidence in humans [18516508, 18459448].

The serotonergic system is well placed to take this role, since it is involved in a broad range of behavioural and physiological functions which commonly participate in response to emotion - apart from the subjective experience of mood, these include sleep, appetite, sexual behaviour and cognition. Anatomically, serotonergic pathways project from the brainstem (midline raphe nuclei) to almost all regions of the brain, including other parts of the brainstem, spinal cord, limbic system, and the cerebral cortex. The system also has different types of serotonin receptors (more than a dozen) specialised to serve different functions and which each have their own genetic controls [18516508].

Impaired serotonin status has been strongly linked to depression, not only lower serotonin levels but also evidence of impaired metabolism, including synthesis, release and reuptake, and with changes to serotonin receptors. Genetic disorders of serotonin metabolism typically include depression as a symptom [18516508 , 15363612, 10665620, 9836013, 8199791, 8159778].

With this background, it is little surprise that tryptophan depletion results in lowered mood, with an increase in irritability or aggression. The extent seems to vary greatly depending on the prior susceptibility of the individual to those mood states, for example more so in women and men with a family history of depression. Indeed, since some classes of anti-depressant work precisely by inhibiting serotonin reuptake at the synapse, this data has been proposed as suggesting that the response of a patient with depression to tryptophan depletion may be predictive of the likelihood they will relapse when they go off anti-depressants. There are also impacts on memory and other cognitive abilities. The opposite effects can be seen with tryptophan supplementation, as well as increased sleepiness and higher pain threshold [2980858, 19721848, 19345451, 1851650, 16862243, 16176613, 11888576, C303, C248].

The cognitive response is made more complex, however, by that contribution of serotonin to sedation and sleep, which can impair performance in some cognitive tests [15206734]. The populist notion that drinking a glass of milk will help with sleep finds some justification in the higher tryptophan content of α-lactalbumin, which has more tryptophan than most proteins [17476368]. On the other hand, a rise in brain tryptophan and serotonin level is also linked to the symptom of 'central fatigue', a symptom whose neural basis is not well understood, but which be seen for example with athletes who overexert, and for which BCAA supplementation has been trialled as a treatment [1748109, 16424146, C101]. Another point of interest is that the cognitive functions affected by tryptophan sometimes have a mood-related dimension, for example, heightened memory for things that have an emotional feeling attached, a phenomenon that has been referred to as "mood-congruent bias" [19939873, 11885569].

A systematic review from 2009 looked at thirty two human depletion studies in relation to memory, attention and executive function and concluded that tryptophan depletion impaired the consolidation of

episodic memory for verbal information, but not semantic, verbal, spatial or affective working memory, had a non-specific or negative effect on executive functions and no or a positive effect on attention, and that the cognitive effects in non-vulnerable subjects were independent of mood changes [19428501].

Another systematic review published in 2010 focused on repletion studies. The authors identified forty three human loading studies with cognitive, mood or sleep outcomes, in both healthy samples and subjects from 'vulnerable' populations (e.g. mental illness). Their conclusion is worth quoting at length: "Reports vary considerably across different cognitive domains, study designs, and populations. It is hypothesised that the effects of Trp loading on performance may be dependent on the initial state of the serotonergic system of the subject. Memory improvements following Trp loading have generally been shown in clinical and sub-clinical populations where initial serotonergic disturbances are known. Similarly, Trp loading appears to be most effective for improving mood in vulnerable subjects, and improves sleep in adults with some sleep disturbances. Research has consistently shown Trp loading impairs psychomotor and reaction time performance, however, this is likely to be attributed to its mild sedative effects" [19715722].

The situation regarding randomised controlled trials of tryptophan in clinical situations such as depression, acute mania, and pathological aggression is not convincing [16268734, C211]. A handful of trials, many conducted over 20 years ago, were too small and heterogeneous to allow any conclusion. Perhaps the best of them was a 12 week RCT conducted in British general practices on 115 patients with depression, comparing tryptophan with amitriptyline, both or placebo. Tryptophan had an equivalent effect to amitriptyline [7156248].

Phenylalanine and tyrosine

These two aromatic amino acids are grouped together because tyrosine is readily synthesised from phenylalanine (less so in infants, in whom tyrosine is conditionally essential). They are substrates for the synthesis of noradrenaline and dopamine respectively.

The literature on dopamine and its role in cognition, cognitive dysfunction, psychiatric and other neurological disorders (including Parkinson's disease) and the various drugs that affect dopamine is vast and well outside the scope of this review. Here we are focused on nutritional influences of these two amino acids. In that respect, there are many similarities between them and tryptophan in relation to the synthesis of their neurotransmitters, but also some differences. The saturation of the equivalent enzyme in the first step converting tyrosine to dopamine is more saturated under normal conditions than the equivalent for tryptophan and more subject to end-product inhibition. Hence, on theoretical grounds, one might imagine that dietary intake of the amino acid would have less influence on neurotransmitter levels. Nevertheless, experimental evidence suggests that it can have some effect, particularly when the central catecholaminergic neurones are very active, as for example during acute stress [19594222, 11291999, 1093382, 6115400, 4276197, C248, C211].

For example, experimentally induced acute tyrosine and phenylalanine depletion (TPD) in healthy humans results in lowered mood and energy, heightened anxiety and reduced executive function, but mainly in a stressful situation, and in one study with evidence of mood-congruent bias [10633491, 16880769, 15688090, C216]. In an interesting experiment using PET scanning, the effects of TPD on spatial working memory and planning were predicted by changes in striatal dopamine levels (although there was no actual impairment of cognition) [16163534]. A decrease in decision making was seen with TPD in patients recovered from depression [15688090].

Conversely, stress depletes the brain of noradrenaline and dopamine [19594222,]. It is therefore not surprising that tyrosine supplements reduced the impact on cognitive tests in healthy volunteers under several types of stress, such as severe cold, sleep deprivation, military combat training, and excess noise [17585971,17078981, 12887140, 10230711, 8293316, 7794222, 2736402]. There is animal evidence that tyrosine supplementation can protect against the cognitive and mood problems caused by weight loss [C216]. It also resulted in changes to cortical and limbic blood flow in one human experiment [17290373]. However, overall the evidence for any kind of clinically significant impact is minimal. A single randomised controlled trial found no clinical benefit for tyrosine as treatment for depression [2142699]. There have been three trials in ADHD (none successful) and a couple in Parkinson's' disease (mixed results) [C216]. A very small RCT found no clinical impact from phenylalanine supplementation in 11 hyperactive boys, but with such a small sample size it is impossible to draw any conclusion from this [3296793].

The story regarding phenylalanine specifically has an additional dimension in the disorder of phenylketonuria (PKU), in which congenital deficiency of the enzyme phenylalanine hydroxylase produces very high blood phenylalanine concentrations and attendant severe mental retardation. Whilst this neurotoxicity does not tell us much about the normal role of the amino acid in cognition, there may be more to learn from the research showing that, even when patients receive early and constant treatment for PKU, they still demonstrate a range of cognitive deficits, in executive function and to a lesser extent non-executive function. These deficits have been interpreted to suggest that, even when treated by phenylalanine restriction, there could be disturbed LNAA transport across the blood-brain barrier and the kind of impact on neurotransmitter and brain protein synthesis that might be expected from the discussions on competitive inhibition earlier in this chapter. This includes possible shortage of the other LNAA in the brain and dopamine deficiency [20123477, 20123470, 20123466, 19191004].

Branched chain amino acids (leucine, isoleucine, valine)

As a class, BCAA can influence neurotransmission via the competitive inhibition of LCNAA brain absorption explained above, Indeed, both animal and human studies have confirmed that BCAA supplements reduce the synthesis of catecholamine neurotransmitters [15930466]. Of the three BCAA, leucine is the most readily transported across the blood-brain barrier and therefore would, in theory, have the greatest potential to cause this inhibition [17721727].

It is worth looking specifically at leucine also in relation to the other CNS functions of amino acids listed earlier in this chapter. Leucine is a source of alternative energy to glucose, via conversion to metabolites that the astrocyte can transfer to adjacent neurones. In addition it regulates enzymes involved in other aspects of brain energy metabolism, as well as participating in the metabolic cycling between glutamate and glutamine, giving it potential influence over glutamatergic neurotransmission [17721727]. Although much less is known about the fate of valine in the brain, it appears to also be used by astrocytes for energy production [19127430].

Although both very high and very low levels of brain BCAA are associated with neuropathology (e.g. maple syrup urine disease) [20301495, 17503711], the clinical randomised trials of BCAA supplements have mostly been in non-cognitive areas, such as athletic endurance, patients with liver disease, intensive care etc. One of those trials assessed mood and cognitive function in runners and found a modest improvement after BCAA compared to placebo [7819652].

Only a few small trials have addressed psychiatric conditions like bipolar disorder and tardive dyskinesia and the evidence is insufficient to derive any conclusion [15930466]. There have been a number of studies in relation to amyotrophic lateral sclerosis, on the grounds that BCAA supplementation will increase the activity of the enzyme involved in metabolism of glutamate and thereby counter the neurotoxic effects of excessive extracellular glutamate that may be a cause of the neurodegeneration in this disease. A meta-analysis of these trials found no basis for therapeutic effect (although that paper was itself withdrawn for reasons that are not clear) [18425887, 14583978].

Glutamate

In one sense, glutamate is at the end of the chain of brain amino acids. This is because of its central role in the major of the excitatory amino acid neurotransmitter systems, and which has a key role in cognition, (particularly memory) as well as in cognitive decline, neurodegeneration and dementia [7482387]. Indeed, it has been said that the brain's handling of amino acids has as its major goals, firstly a steady supply of substrates available for the synthesis glutamate for glutamatergic systems and secondly, to regulate the concentration of glutamate in the extra-cellular fluid. That concentration has to be kept low in order to minimise the signal-to-noise ratio at the glutamatergic synapse and to prevent excitatory toxicity [15930465].

The primary source of neuronal glutamate is glutamine, which is synthesised in astrocytes and converted to glutamate within the neurone. But glutamate is part of a complex biochemical web in which it can be synthesised from, as well as contribute to the synthesis of, various other amino acids. For example, common precursors are the branched chain amino acids, particularly leucine, and to a lesser extent alanine. Glutamate in turn serves as the precursor for the synthesis of the inhibitory neurotransmitter GABA, as well as aspartate. Animal studies show that glutamate (along with GABA, glycine and taurine) also modulate serotonin synthesis and release. Moreover, the astrocytes are not mere factories to produce glutamate, but play an active regulatory role over the activity of the neurones by varying the amount they

release of glutamate, serine and other amino acids [20633599, 11053233, 7805588, 7693110].

Neurones immunoreactive for either glutamate or GABA make up most of the non-glial population in the cortex. Each has several families of receptor, apparently serving different functions and subject to different genetic encoding. Glutamate receptors are divided into two categories - ionotropic and metabotropic, (based on whether they respond to stimulation by opening an ion channel directly, or use second messengers to indirectly open one). The most prominent of the former is the NMDA receptor, whilst the metabotropic glutamate receptor 7 has been described as “an important regulator of glutamatergic function, of fear and aversion and cognition and thus....an innovative therapeutic target for stress-related disorders at the interface of cognition and anxiety” [20371242]. Since glutamate is excitatory and GABA inhibitory, the two interact in many parts of the brain to maintain balance between those two `forces’. Imbalance, on the other hand, can have pathological consequences, in part because excess excitatory activity is of itself neurotoxic. The consequences have been postulated to include Alzheimer’s disease, schizophrenia, anxiety, insomnia, depression and addiction [20970118, 20688449,, 20021448, 18322401, 17617664, 12835112, 11532718, 7805588].

This balance between excitation and inhibition, as has been discussed in the chapter on zinc, is central to formation of memory. The neurophysiology of long term potentiation (LTP, the mechanisms believed to be involved in memory) involves, after various biochemical intermediate steps, an enduring heightened post-synaptic response to glutamate release at specific synapses. On the wider brain architectural level, this LTP is in balance with long term depression (LTD) of synaptic activity, both of which are required for overall brain plasticity [1553102]. This balance involves, in part, interaction between glutamate not only with GABA, but also with the monoamine neurotransmitters serotonin, noradrenaline and particularly dopamine. Hence the relevance of those interactions for memory [C495].

Based on this underlying biochemistry there is potential for dietary amino acid intake to influence this regulation of the excitatory amino acid mechanisms, and thereby influence cognition [12575816]. How true this is in reality is yet to be determined. There is evidence from animal experiment that dietary variation of protein:carbohydrate ratio can affect GABA-glutamate metabolism within the hippocampus in ways that vary with age [17263091]. On the other hand, the fact that glutamate is so interconnected with a variety of amino acids, and that its concentration appears to be tightly regulated by mechanisms within the brain and within individual neurones, both suggest that any dietary influence would be muted.

There have been a few small, therapeutic trials using GABA to treat insomnia and stress, too few to support any conclusion [19594222].

Other amino acids

Animal studies and a handful of human ones have reported on the impact of dietary **histidine** on brain histamine and of **threonine** on spinal cord function and mood (glycine is itself a neurotransmitter, particularly in the spinal cord). These do not add up to any clinical conclusion [C211].

Glycine is a non-essential amino acid that can synthesised from **threonine** and **serine**. It is of particular interest because it has a specific function binding to NMDA receptors and thus exerts influence on glutaminergic cognitive functions. Most human glycine supplementation studies have not found any obvious cognitive effects (although one reported EEG changes), and medications that target this binding site have been tested for schizophrenia. A few trials of glycine supplements for schizophrenia and OCD have been reported [20182547, 18455219, 17972276, 17952411, 15205876, 11806864, 10704956, 9668194, 8837983, 8037263, 7793190]. Threonine, serine and their kinases and phosphatases are also important in formation of memory, being examples of the general process by which the interplay between phosphorylation and dephosphorylation of proteins within the brain is used to regulate brain plasticity, in this case particularly in the hippocampus [17084465, 15626492, 11433371].

Arginine is precursor to the vaso- and neuroactive nitric oxide. Given together with lysine to high trait anxiety individuals, it resulted in enhanced ACTH, cortisol, adrenaline and noradrenaline levels and galvanic skin responses during stress compared to placebo in a human RCT [16117182].

Taurine is a semi-essential amino acid which has a particular role in energy metabolism but is also found in high concentration in the retina, where it seems to exert some kind of tropic role, though exactly what is not yet known. This may also apply to other parts of the brain, such as the hippocampus [14553911, 12000086, 11843263].

Meat

A brief review of the research on the cognitive associations of consuming meat (and to some extent other animal food sources) in the diet is included here for convenience. This section will necessarily be short, because clearly it is impossible to separate the impact of meat consumption on cognition from the effect of the many nutrients that meat is rich in, and very difficult to do so from the effect of eating less of the foods that meat displaces in the diet, or for meat eating being a marker for generally less healthy diet, let alone from the socioeconomic correlates that go with eating more meat [17964314]. In short, observational studies have very limited capacity to delineate a direct cognitive effect of meat itself.

So far as the nutrients are concerned, these have been dealt with separately elsewhere in this review, for example protein, iron, zinc, vitamin B_{12} etc . Meat can also make a significant contribution to essential fatty acid intake, with the LCPUFA profile depending on the type of meat (e.g. grass vs grain fed), and this might be very relevant to cognition [20219103, 19055853, 16289978].

Given what is shown throughout this review concerning the importance of each one of those nutrients to cognition, it would be an obvious deduction that consumption of lean meat would support cognitive health in all age groups. Indeed, there are those who argue that the regular consumption of meat has been an essential prerequisite to the evolution of the human brain, because of its density of energy and LCPUFA, amongst other things (the latter issue was reviewed in the relevant chapter) [10918988].

Observational studies show that animal protein intake is associated with cognitive function, for example with earlier attainment of motor milestones in infants in Nepal and Guatemala, with psychomotor developmental indices at 24 months in American children, and maternal meat intake was correlated with habituation behaviour in semi-rural Egyptian subjects [1897473, 16317129, 15572888, 15570028]. The latest and by far the largest study of this sort was conducted in China. It was a cross-sectional design on 20,086 adults (≥50 years of age). After adjusting for socioeconomic and other potentially confounding variables (but presumably not for faulty memory of their eating habits fifty years or so earlier), childhood meat consumption was associated with current word recall (mean of 0.22 extra words recalled) [20526800].

At the other end of life, there was no association between meat consumption and incidence of dementia in a French elderly population [12399342].

There is however some limited RCT data to inform this matter, from a research group in Kenya. In a controlled trial randomised by school, meat supplementation of the diet for 2¼ years brought about greater improvement in various cognitive and academic results than vegetable supplementation or control. In an earlier report from the same research group, children given meat has less periods of low activity and more leadership behaviour and initiative than children provided with vegetable foods [17374691, 14672294, 16075570].

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Chapter xx: IRON

Executive summary

Iron is found widely in the brain, particularly in oligodendrocytes and in areas associated with dopaminergic systems, including the hippocampus. It is involved in three main brain functions:

1. Neurotransmission: dopamine, GABA, serotonin and norepinephrine.

2. Neuronal energy metabolism

3. Myelin synthesis

Maintenance of the appropriate local iron concentration is crucial to iron's function and to avoiding the damage that excess iron can cause as a pro-oxidant. This is maintained by complex, active homoeostatic mechanisms operating in association with the blood-brain barrier.

Animal studies show that iron deficiency causes damage to structure and connections of neurones, to neurotransmitter secretion and receptors, and to myelination. Damage may not be completely corrected if iron deficiency occurs during critical neurodevelopmental periods.

There have been well over a hundred human observational studies on the association between iron status and cognition. More than 80% of them show some association, including with impairment to EEG and evoked potential measures of neurotransmission. However, less than a fifth of these studies were prospective, most were with small subject numbers or in populations at risk of poverty, poor educational opportunities and general ill health. This gives rise to substantial risk of confounding.

Over 75 separate human clinical trials on over 22,000 subjects have been reported, although only a minority were randomised, controlled and blinded. The large majority were in children. In two thirds of these trials supplementation produced at least one positive cognitive outcome. Four separate meta-analyses have been published, each with a different focus, collectively including 32 of these trials on nearly 7,000 subjects. Their respective conclusions were:

1. No convincing evidence of short term benefit in treating pre-school children with IDA.
2. Modest mental score improvement in children, in trials having various baseline iron status.
3. Some evidence of improved attention and IQ in subjects with undetermined baseline iron status.
4. Limited evidence of improved motor but not mental development or behaviour in preventive trials.

Taking all the evidence into account, we can conclude that:

1. Iron deficiency can cause serious cognitive damage, including mental, motor, language, overall IQ and emotional parameters. This is particularly so when it is severe, prolonged, and occurs during vulnerable periods (foetal and early childhood). Some of these effects suggest impaired neurotransmission and involvement of the dopaminergic system.

2. Correction of iron deficiency is likely to improve cognition in children, particularly motor development, but may not reverse the damage entirely, especially in the exacerbating circumstances outlined in point 1.

3. There is modest evidence for cognitive effects of iron deficiency in adults and benefit from supplementation, even in the absence of anaemia. There is very little evidence in elderly subjects.

4. For these reasons, bearing in mind how common iron deficiency is and the benefits seen in the majority of prevention trials, every effort should be made to ensure adequate iron status during childhood (including adolescence). It would be prudent to also apply this to higher risk adults (e.g. reproductive age women, those on restricted diets etc).

Physiology

Iron is the most abundant mineral within both the body and the central nervous system.

Because of its wide range of potential oxidation states, and hence its chemical reactivity, iron is well suited to modulation of a wide range of functions in the body, in most cases in association with proteins. For example, the non-enzymatic compounds haemoglobin, myoglobin and cytochromes, and a considerable number of enzymes (e.g. flavoproteins). The general function categories of these iron-containing proteins are oxygen transport and storage, electron transfer in the production of ATP, and substrate oxidation-reduction, usually so as to protect cells from oxidative damage. It has a role in DNA synthesis 11160590, 17413089, C203.

Iron, ferritin and transferrin are all distributed widely through the brain, with the majority being found in the supporting cell type directly involved in myelin production, the oligodendrocyte C274, 8776576, 1529678, 12704220. C274. There are certain areas with much denser iron concentrations (approaching that seen in the liver), such as the nucleus accumbens, substantia nigra, deep cerebellar nuclei, the red nucleus, and hippocampus - see Fig. F1 12704220 , C445. Another perspective on the densest iron concentrations is that they are in areas associated with dopaminergic-peptidergic neurotransmission 10721903.

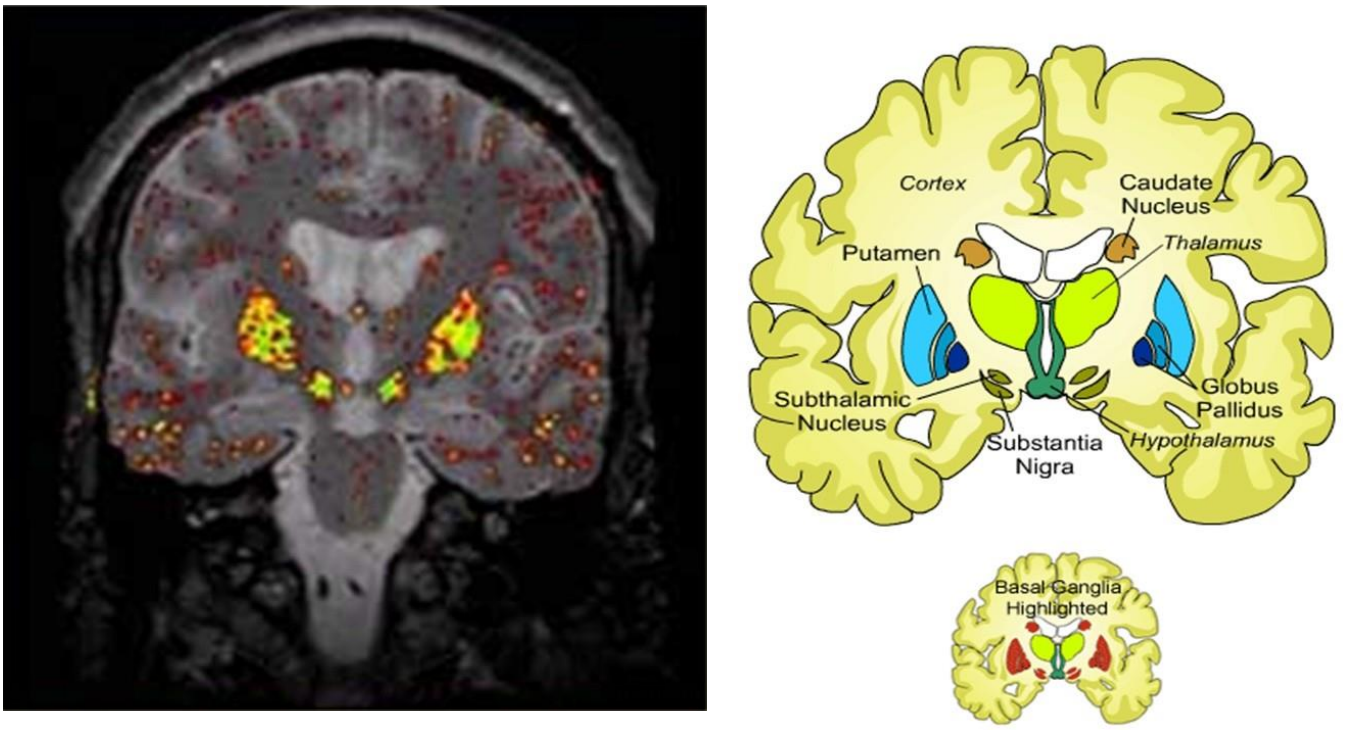

Fig. F1. Distribution of iron in the brain: MRI on L., matched anatomical areas described on R. (image from C445)

There are specific mechanisms for transport of iron into the CNS, across brain endothelial cells, much of it involving transferrin, receptors for which are found in neurones but appear not to be found in astrocytes 12553165, 17953660, 17551833. Astrocytes are, however, thought to play a vital role in the iron regulation, absorbing iron mostly as non-transferrin bound, storing it in ferritin, and exporting it by a mechanism that involves ferroportin and ceruloplasmin 17551833, .

Iron deficiency also appears to have especial importance in the hippocampus, reflected in particular abnormalities seen there in iron deficiency, associated with disturbances in zinc metabolism 18790724.

Brain function

Within the brain, iron has three main functions C203, 8094018, 12704220, C203, 11160590:

1. *Monoamine neurotransmitter systems*: dopamine, GABA (γ-aminobutyric acid), serotonin and norepinephrine. Both development and function of these systems are influenced by iron-dependent enzymes in their synthetic pathways, receptors, and reuptake transporters. For example, the enzyme tyrosine hydroxylase. Iron may also have some role in glutamate secretion, for example in the retina 15613494.

2. *Neuronal energy metabolism*: iron is incorporated into cytochromes and mediates oxidative phosphorylation of ATP.

3. *Myelin synthesis*: both because it supports energy production in myelin-producing oligodendrocytes and possibly due to the role of iron-dependent enzymes in fatty acid metabolism.

Iron homoeostasis

The ability to store a ready, bioavailable amount of iron is essential to brain function 11551742. Homeostasis is crucial because excess iron (and probably ferritin independently) is potentially very toxic, acting as a pro-oxidant. The challenge of maintaining that homoeostasis, separated from the rest of the body by an efficient blood-brain barrier, requires sophisticated, complex mechanisms 11160590, 17953660. This control is highly dynamic, ensuring each functional area and cell type receives the right amount of iron at the right time. Iron moves about the brain within the cerebrospinal fluid (the choroid plexus secretes a good deal of transferrin) 11160590, 1993336 and the brain obtains it via transferrin receptors on the endothelium of the cerebrovascular system. This is a highly selective process, which increases brain iron uptake when body iron is low and vice versa 12704220. Thus, up to a point, there is a `protective buffer' insulating the brain from body iron deficiency. Brain iron uptake is not reflective of the overall blood-brain barrier permeability 11160590.

Disturbances of this `iron management system' result in both decreased metabolic activity and increased vulnerability to oxidative damage C264 . A variety of mechanisms serve to contain this pro-oxidant potential, for example there are ferroxidase enzymes within the brain, such as ceruloplasmin, that oxidise the toxic ferrous iron (Fe++) to its non-toxic ferric (Fe+++) form 12151537. At the same time, and as with zinc, it is possible that the pro-oxidant neurotoxicity of iron may actually serve an important purpose in terms of brain plasticity 12835112.

A curious side-light to this story is the condition of 'restless leg syndrome', a neurological disorder which in its primary, genetic form appears to be due to dysfunction of the postsynaptic dopamine receptors, related to disturbances of those iron homoeostatic mechanisms, such that there is impaired transport of iron from serum to CNS and reduced expression of transferrin receptor 18460286 , 15743333 ,15675724, .

Iron in development

The distribution of iron in the brain described above applies to the mature adult state. Iron needs vary during different stages of development, and so the distribution of iron also varies. Iron content in the brain is lowest at birth, and increases with age reaching adult levels only at puberty 11930085. The requirement for iron increases during the post-weaning phase as myelination begins, a process that is not complete for some parts of the brain until early adult life C207, 19002191, 18833009. In humans, the toddler period (from around 6 months to 2 years of age) is a time of profound hippocampal and cortical development, associated with intense learning of higher order skills 16770951. This also happens to be a high risk period for iron deficiency, as neonatal stores are used up and bioavailable iron-rich food sources such as meat may form a relatively smaller part of the diet 16356022, 19174983.

Animal experiments show that sensitivity to the effects of iron deprivation thus also vary 12704220. However, in general the impact of iron deprivation at the anatomical and biochemical level during critical periods of brain development can be deduced from its main CNS functions listed above - hippocampal structure and function, monoamine metabolism and myelination 19021538. These are especially prominent in the hippocampus and striatum, two areas of the brain that are particularly sensitive to iron deprivation during foetal and early neonatal life.

The literature on animal studies on iron in the brain and the effects of deficiency is truly vast and far beyond the scope of this review. It has been comprehensively summarised in various papers C356, C203, 7901870. Very briefly, changes in the brain observed in animals when they are iron deficient during

brain development include decreased arborisation of dendrites resulting in a decreased number and complexity of inter-neuronal connections (and associated with decreased expression of neurotrophic factors), changed location and function of oligodendrocytes resulting in demyelination of the neurones, and adverse effects on the synthesis and catabolism of dopamine, GABA and norepinephrine [20089786, 19022978, 17374674, 17546681, 17182811, 16669598, 16187331, 15909765, 15352214, 14966382, 14614257, 12730445, 12672939, 12401959, C207]. For example, there is disrupted proliferation of glial precursor cells and generation of oligodendrocytes from them [12191838]. There are also changes in the visual tracts [19000382].

In terms of brain function, these animals show impaired learning, and many and varied behavioural alterations [9597172]. Iron-deprivation of rats during the perinatal period results in impaired sensory and locomotor abilities, altered behaviour (e.g. more hesitant in novel settings) and reduced learning [18424604, 17592938, 17182811, 16713640, 16603209, 16117187, 9166875]. There is a disturbance in sleep pattern with increased wakefulness during darkness and reduction in both REM and non-REM sleep [17098470]. There is some evidence of effects on gene and gene expression profiles [17447428, 18297894].

There are limits in how much such studies can be applied to humans, particularly since rats have different rates and stages of neurodevelopment [9597172]. An animal that is `closer to home' is the monkey, and monkeys subject to iron deprivation display altered emotional and behavioural characteristics, including more lability in response to novel environment. When the iron is lacking prenatally there was also an impact on attenuated inhibitory response later on when the monkeys had grown to be juveniles [16343844, 17374664].

Crucially, although brain iron can be replenished after experimental deprivation, it may not fully normalise if the deprivation occurs during the critical periods of development [18297894, 864518,]. And the functional and anatomical deficits often can never be repaired [16713640, 15909765, 12672939, 11160552, 11160590, 12704220, 8598555, 864518]. As an example, previously iron deficient monkeys tested at 9 months of age still showed cognitive deficits, despite their iron status having been corrected [18300719]. Long-term effects are seen in all three main areas of deficit referred to above [19021538,]. Exactly why the damage cannot always be fixed is not fully understood, but may relate to permanent changes in neurotransmission, for example due to irreversible changes to receptors or compromised myelination [11930085, C112]. It does appear to depend on whether iron status is corrected before a critical window closes [18297894]. So, for instance, early postnatal iron supplementation reversed the neuropathological effects of gestational iron deficiency in rats [17449578].

In interpreting the animal experiments, one should bear in mind that the kind of experimental iron deficiency inflicted upon the rats from whom this data was obtained was generally rather severe, so it is not clear exactly how applicable this is to the kind of iron deficiencies more normally seen in humans, especially in the developed world where mild to moderate levels of iron deficiency are the more common [11930085].

Human depletion studies

There have not been many human depletion studies that have specifically looked at cognitive effects. In seven men undergoing deliberate iron depletion through repeated phlebotomy, there was no consistent impact on cognitive performance, although four of them showed decline in EEG power in the occipital area [7178279]. An inadvertent depletion study may have been conducted by an individual who gave blood every two weeks for 6 years. He developed iron deficiency without anaemia, and had symptoms of short-term memory loss and depression which improved markedly after his iron status was corrected by supplementation [18937740].

Human observational studies

Iron deficiency has been associated with cognitive and developmental deficits in more than a hundred observational studies . These have been reviewed by many authors (e.g. [18297894, 11160596, 17413089, 16770951, 3962908]), and are so numerous that they can best be dealt with as the summary appearing in **Tables F1** and **F2**.

Table F1: Characteristics of iron observational studies in Table F2 (N=115)

	% of studies	Subject n
Study design		
Cross sectional	76%	
Case-control *	5%	
Prospective	19%	
Clinical criteria ****		
Iron status	10%	
Haemoglobin	2%	
Iron status + Hb	2%	
Iron deficiency	22%	
Iron deficiency anaemia	33%	
ID + IDA	13%	
Anaemia (iron status not stated)	18%	
Subject number		
<100	49%	
100-249	22%	
250-499	11%	
≥ 500	18%	
Age group		
Neonates	7%	7,655
Pre-school children	53%	23,774
Primary school	13%	9,840
School aged	6%	252
Adolescent ***	4%	1,043
Adult (≥ 18 yrs) ***	11%	31,671
Elderly	6%	3,555
		77,790
Low	52%	70%
Intermediate	22%	4%
High	26%	26%
Socioeconomic risk ****		
Some significant association	82%	
No significant association	20%	

As far as practical, each study has been counted only once. Where different arms of one study each require inclusion, subject numbers are not double counted.

* Case-control in regard to a clinical condition other than iron status/anaemia

** Clinical criterion regarding iron or anaemia as used in analysis or sample selection. Studies with combined criteria counted in combined category only.

*** Except for one study of 15-30 yr olds (n=255) which is included under Adolescent. Note that the n for adults include a single study of 28,834 subjects.

**** Socioeconomic risk is based on country of origin, not individual study sample circumstance

Table F2: Observational studies on iron deficiency and cognitive outcomes: in children

PMID	Sample	n	Dsgn	Country	Iron status	Outcome	Supp
Mother/neonates							
19158210/ 15795446	10/52 post-partum	95	X	South Africa	IDA (maternal)	Responsiveness, hand-eye movement, quotient in infants. Maternal sensitivity	Pre
15671224	9/12 post-partum	81	X			Cognition (Digit Symbol), anxiety, stress, depression in mother	Post
Neonates							
15318248	Birth	53	X	Israel	ID/IDA	Higher % abnormal reflexes	
15155871	Birth -> 1yr	51	P	USA	ID	Impaired auditory recognition (ERP) at birth, motor skills at 1 yr	
20183732	Birth -> 3.5 yrs	40	P	USA	ID	Impaired memory	
15732057	Neonates	185	X	Peru	IS/Hb	Emotionality (controlled for confounders)	
18838630	Neonates + adult	6,872	C	USA	ID	Schizophrenia	
Young children (to 2 yrs)							
16044827	Infants	54	X	Japan	IDA/past IDA/IR	Bayley SID, Enjoji Scale	
17290568	Infants	93	X	Turkey	ID/IDA	No diff in auditory brainstem evoked potential (ABP)	Pre/post
11301221	Infants	40	X	Turkey	IDA	No diff in auditory brainstem evoked potential (ABP)	
15911010	3-36 mo	56	X	Turkey	IDA	ABP, when with protein-calorie malnutr	
15499963	6 mo	108	X	Turkey	ID/IDA	Denver + Bayley SID	Pre
19327925	8-24 mo	50	X	India	IDA	Correl betw. IDA severity and VEP latencies	
18510805	3-15 mo	40	X	Mexico	IDA	Cognition, fine motor and social/emotional, EEG changes	
18029495 15795440	5-19 mo 6-18 mo	771 646	X C	Zanzibar	ID/IDA ID/IDA	Motor activity Walking but not crawling	
3987574	Infants -> Grade 2	75	X	Israel	IDA	Learning achievement, positive task orientation	
6183419	Infants		X	Guatemala	Anaemia	Motor development, mental test scores for those > 19 mo old	
3722390/ 2580861	6-24 mo	42/ 68	X	Guatemala	Anaemia	Spatial relations, increase in mother-baby body contact/ Mental scores in 10 infants with abnormal affect	
15526591	6-24 mo	120	X	Bosnia	Anaemia	Bayley SDI	Pre
17766529	6.5 mo + alcohol abuse in mother	96	P	South Africa	IDA	Head circumference	
19640971	4-12 mo	193	X	Mexico	ID, anaemia	Activity	

PMID	Sample	n	Dsgn	Country	Iron status	Outcome	Supp
11369562	8 mo -> 18 mo	1,181	P	UK	Anaemia	Griffiths Scales of Mental Development: locomotor sub-scale	
18022771	6-18 mo	1,444	X	Nepal, Zanzibar	IDA	Sleep duration and night waking	Pre/post
20335633	9-10 mo	61	X	USA	ID/IDA	Lower eyeblink rate in IDA	
19592115	9-10 mo	9	X	USA	IDA	Upper-extremity control	
20431398	9-10 mo	68	X	USA	IDA	Maternal-infant interaction	
17671043	9-12 mo	34	P	USA	IDA	Attention and recognition memory	
18410777/ 18272298	9-10 mo Afro-Am	77	X	USA	ID/IDA	Social-emotional behaviour, motor function	Post
C367	9-12 mo	38	X	USA	ID	Solemnity	
2596947	10 mo-4 yr	147	X	France	ID/anaemia	Development Quotient in anaemic subjects only	
2183661	11-15 mo	196	X	Spain	ID/IDA	No assoc. with psychomotor development	
7322719	11-30 mo		X	USA	ID	No differences, except isolated differences in fear, sensory interest	
10088991	12-24 mo	132	X	Guatemala	Anaemia	Behaviour	Pre
12800379	12-60 mo	64	X	Turkey	IDA	ABP	
2472596	12 mo	196	X	Chile	ID/IDA	Bayley Mental, Psychomotor Developmental scores in IDA only	During
C358	12 mo	62	X	USA	IDA	No assoc. with mother-child interaction	
925276	1 yr	198	X	USA	Hb	No assocation with Developmental Screening Test	
7678046	12-18 mo	50	X	Indonesia	IDA	Bayley Mental and Psychomotor scores in IDA only	Pre
6834185	15 mo	37	X	Chile	ID/IDA	Bayley Mental scores in IDA only	Pre
16317129	17 mo	485	X	Nepal	Anaemia	Onset of walking	
8820586	18-30 mo -> + 6/12	42	P	USA	ID + lead overload	Cognitive development	
3783750	Birth -> 5 mo	65	P	USA	IDA	Borderline link irritability with higher TIBC	
3701513	18-60 mo	50	X	USA	IDA	No differences in cognition	Pre
3767413	22 mo, Asian origin	145	X	UK	Anaemia	Fine motor and social development	
Pre-school (to 2 yrs)							
1432416 7523846	2 yr 4 yr	392 332	X P	Yugoslavia	Anaemia	Mental Development Index (independent of lead status) Changes inconsistent by 4 yrs	Post
14767350	2 yr/ 4 yr + prenatal cocaine exposure	417	X/P	USA	IDA	Full Scale IQ	Post (n=122)
1613117	2-5 yrs (Hispanic)	236	X	USA	Hb	Behavior problems, social withdrawal, sleep problems, depression	

PMID	Sample	n	Dsgn	Country	Iron status	Outcome	Supp
C150	2-6 yrs	44	X	Brazil	IDA	Language development	
3962908	30-72 mo	153	X	Guatemala	ID	Discrimination learning	
15226754	3-4 yrs	49	X	Greece	IDA	No assoc. with cognitive test scores	Pre
19267294	3-5 yrs	112	X	USA	IS	Vocabulary and verbal scores	
17197281	3-5 yrs	42	X	USA	IS/Zn/Pb	Interacn between iron, lead and zinc on cognitive scores and behavior	
17311960	47-68 mo	238	X	India	IDA	Affect and behavior.	
C161	Ave 4.1 yr	112	X	USA	IS	Peabody Picture Vocabulary Test, MCSA verbal scores	
20513281	4-6 yr -> 1 yr later	7,331	P	China	Anaemia	Chinese Wechsler IQ	
C440	Children	130	X	China	IDA	Attention, learning	Pre
C438	6-36 mo	333	X	China	IDA	Developmental quotient	Pre/post
17916959	4-10 yrs	89	X	Argentina	IS	Visuomotor ability	
15583094	4-14 yrs + ADHD	53	C	France	ID	More severe general ADHD symptoms	
3196075	4-14 yrs + mental retardation	77	C	Venezuela	IS	Association with mental retardation	
Primary school children							
12074177	Ave 9.6 yrs	427	X	Thailand	IDA	Cognitive function, no assoc. with ID alone	
16585816	9-14 yrs	230	X	India	Anaemia	Digit span and visual memory	
9368806	9-13 yrs	800	X	Jamaica	Anaemia	No association with academic achievement	
2773846	9-11 yrs	1,358	X	Thailand	ID/IDA	No association with IQ, language, maths	Pre/post
18571983	8-10 yrs		X	Mexico	ID	Working memory	Pre
18279203/ 19592115	7-13 yrs + ADHD	52	X	Turkey	ID	Hyperactivity, no impact on cognitive performance	
18316268	6-8 yrs	602	X	Mexico	ID/IDA + Pb	No signif association with sleep, behavior, activity	
14747673	6-8 yrs	724		Mexico	ID/IDA + Pb	Cognitive performance	
11389261	6-16 yrs	5,398	X	USA	ID	Math scores	
17691592	6-12 yrs	30	X	Turkey	IDA	Total IQ	Pre
10495210	6-12 yrs	100	X	Mexico	ID	WISC: Information, comprehension, verbal, performance and full scale IQ, slower EEG power spectrum	
17447429	10 yrs		X	Israel	Rx'd ID as infants	ABP, general IQ, reduced morning cortisol	Post
4698956/ C352/C353	12-14 yrs Afro-Am		X	USA	Anaemia	Scholastic performance test, visual processing, behaviour	

PMID	Sample	n	Dsgn	Country	Iron status	Outcome	Supp
4072957 2773844	Ave 11 yrs	119	X	Indonesia	IDA	School achievement, visual attention, concept acquisition no assoc. with Raven Progressive Matrices IQ	Pre
14132974	Children	56	P	USA	IDA	Behavioral problems	
18165896	Children/adolescent + ADHD	196	X	Turkey	ID	Behavioral problems	
Infants followed up over long term							
11865266	Birth -> 5yr	278	P	USA	ID	Language ability, fine-motor skills, and tractability.	
9499554 2438638 8804327	12-23 mo -> +3, +6 mo	191 86	X	Costa Rica	IDA	Bayley mental and motor scores, emotion, social interaction, playfullness and attentiveness Mental scores at each point	Pre Pre/post
17041272 1870641 C361/C454	-> 5 yrs -> 10-13 yrs	142 167	P			Physical activity, positive affect, verbalization, mother-child reciprocity Mental and motor functioning (controlled for socioeconomic status) Incidental learning and abstraction, motor	Post
19736288 17050023 10742372 16966351	-> 11-14 yrs	185 182 159				Externalizing and internalizing problems Motor scores, school achievement, spatial memory, selective recall, tachistoscopic threshold Prolactin response	Post
C452	-> 15-17 yrs	184				Motor and cognitive test performance	
17088512 20406573	-> 19 yrs	185				Cognitive scores through to 19 yrs old, incl. cognitive tests of frontostriatal, hippocampal function	Post
12441207 11872311 9734748 12538778 17570059 17957147 C372/C354	6 mo -> 18 mo -> 4 yrs -> 10 yrs	35 26 55 64 44 55 58	X P	Chile	IDA	Increase in 24 hr motor activity, no longer so after treatment Reduced motor activity during waking ABP Sleep: delayed EEG spindle patterns, altered REM sleep and temporal organization, ABP, VEP Nocturnal sleep consolidation. executive function	Pre/post
C350	6-18 mo -> 7 yrs	61	P	USA	Anaemia	IQ, clumsiness, attentiveness	Post
16584658	9 mo -> 5yrs	55	P	Portugal	IDA	No assoc. betw. IDA at 9 mo and psychomotor development at 5 yrs	Post
6840745 3987574	9 mo -> 5yrs	873	P	Israel	Anaemia	Development quotient	
C366 8779619	1 yr -> 5.5 yrs	77 35	P	Chile	IDA	IQ, VMI, motor, language proficiency neurological maturity Activity, more inhibited and timid	Post
17407463	1 yr -> 6 yrs	77	P	Iceland	ID	Fine motor development still at age 6 yrs	
9925132	13 mo -> 10 yrs	5,411	P	USA	Anaemia	Mild or moderate mental retardation (controlled for confounders)	

PMID	Sample	n	Dsgn	Country	Iron status	Outcome	Supp
Adolescents							
19999786	13-15 yrs	188	X	Sri Lanka	ID/IDA	No assoc. with educational performance or intelligence.	
C436	15-17 yrs	148	X	Japan	IS	No assoc with educational performance	
9710844	15-30 yrs	255	X	Australia	ID	No assoc. with psychological distress.	
16025871	15-18 yrs		X	Sweden	ID	Dizziness, irritability, depressive symptoms	Pre/post
9503079	13-14 yrs	452	X	Jamaica	Anaemia	School achievement	
Adults							
C266	Young adults	297	X	UK	ID	No assoc. with cognitive test scores	
18574611	22 yrs	28	X	Egypt	IDA	Cognitive tests (MMSE, WMS-R, and WAIS-R),ERP, EEG abnormalities	Pre/post
6691286	University students	69	X	USA	ID	EEG: L vs R hemisphere, verbal fluency but better non-auditory task	
3800306	University students	172	X	Australia	ID	Spatial performance	
17063146	Med. student women	192	C	Iran	ID	Lower ferritin in depression	
11190004	18-23 yrs women 45-50 yrs women	14,762 14,072	P	Australia	Self-reported ID	Mental component of general health, vitality	
17344500	18-35 women	149	X	USA	ID/IDA	Processing speed (IDA), accuracy (ID)	Pre
16826432	Adult women	92	X	Japan	Anaemia	Vitality and general health scores	
18689568	17-38 yrs women	543	X	France	ID	No assoc. with mental component of SF-36, vitality	
18423335	Adults	51	X	Turkey	IDA	P300 and EEG power spectra	Pre/post
12947438	Menstruating women	865	X	France	ID	No assoc. with mental health, less memory disorders	
10401535	Pre-menop women	365	X	USA	ID	No assoc. with depression	
9683334	Dieting women	14	P	USA	ID	Attention	

PMID	Sample	n	Dsgn	Country	Iron status	Outcome	Supp
Elderly							
2360555	> 60 yrs	28	X	USA	ID	Inconsistent assoc. with EEG patterns	
15866252	Heart failure	1,511	X	Italy	Anaemia	Cognition	
16970654	70-80 yrs	364	X	USA	Anaemia	Executive function	
15207438	Cognit impaired	35	C	Italy	ID	Higher ferritin in impaired group	
20182059	Probable dementia No dementia	51 749	P	Australia	ID	No assoc. with cognitive scores in either group, or with presence of dementia	
2735676	Cognit impaired	254	X	USA	ID	No assoc. between degree of impairment and iron status	
18382689	65-84 yrs	817	X	Italy	Anaemia	Selective attention	

n: based on intention to treat, i.e. subject numbers commencing intervention
Age: - = range of ages, -> = prospective to this age**,**
Design: X = cross-sectional, P = prospective, C = case-control (in regard to clinical condition other than iron status)
Iron status given for measure shown in outcome column, when this is part of design or sub-grouping in analysis. ID= iron deficiency, IS= iron status, IDA=iron deficiency anaemia.
Outcome: Except where stated, ID assoc. with worse outcome on these parameters, ABP = auditory brainstem evoked potential, ERP= event-related potential, VEP = visual evoked potential.
Supp: when is observational element of supplement trial, indicates which phase. Note that being a trial does not necessarily mean a controlled trial.

Maternal-foetal iron deficiency

It is more feasible to individually (but briefly) mention the much lesser number of studies relating to iron deficiency during pregnancy. A developing foetus is obviously dependent for its iron on supplies from the mother, but foetal iron deficiency can arise from conditions other than maternal deficiency. These include maternal circumstances that restrict foetal iron transfer (for example smoking and hypertension) or conditions which increase the baby's *in utero* iron requirements (e.g. diabetes which increases foetal size and hence mass, as well as giving episodes of foetal hypoxia to which the baby responds by increasing erythropoiesis) [19021538, 17157088]. Prematurity often results in low iron stores in the newborn, despite adequate maternal levels. This occurs because, although the baby's iron concentration may remain `normal' (75 mg/kg body weight throughout the third trimester), a good deal of its iron stores are accumulated during the last trimester, so that the limited total amount of iron stores of a premature infant will be used up during rapid post-natal growth [17157088, 17413089, C203].

Complicating the picture is the likelihood that iron deficiency will itself adversely affect the pregnancy, and that the disturbed pregnancy, rather than the iron deficiency, might bring about the cognitive defects. For example iron deficiency can cause maternal and fetal stress, thus stimulating corticotropin-releasing hormone, something known to be a major risk factor for preterm labour, premature rupture of the membranes, pre-eclampsia and eclampsia [11160591]. In reality, many pregnancy conditions that fit under the category of uteroplacental insufficiency or hypoxia are associated with low cord ferritin [3612404], and maternal anaemia before mid-pregnancy is associated with an increased risk of preterm delivery and lower birthweight [10721924, 7890339]. On the other side of the size `coin', large-for-gestational-age infants - the commonest cause of which is impaired glucose tolerance during pregnancy - may have lower ferritin levels, due to redistribution of available iron rather than dietary shortage [2782069]. Any one of these pregnancy conditions could directly affect foetal brain development. In addition, severe maternal anaemia is associated with disturbances in hormonal levels that could also potentially affect the baby's brain, such as thyroid hormone and prolactin [18272016]. High serum prolactin levels in infants exposed to stress during pregnancy have been linked with hesitancy and unhappiness during developmental testing [7893857].

Focusing on the most common of these mechanisms - maternal iron deficiency - the first question is to what extent maternal iron deficiency does bring about foetal iron deficiency. Certainly the baby will enjoy a substantial measure of protection by the preferential routing of any available iron to it rather than to the mother [11930085]. Whilst there may be only a slightly relationship between maternal haemoglobin late in pregnancy and cord haemoglobin [10799402], it is a different matter in relation to more direct measures of iron status. Although not extensively researched in humans, such data as there is suggests that an iron deficient mother, even if she is not anaemic, may well produce an iron deficient baby, particularly when the iron deficiency is severe [16099345, 17157088, 15776614, 10088634, 10799402]. Two studies - one Indian, the other from Mexico, found that low maternal iron status was linked with low cord ferritin [8955460, 16099345]. On the other hand, a study from Jordan did not [10405849]. (Studies of foetal iron status are usually based on cord samples taken at delivery).

Another factor to be taken into account in considering cognitive effects is that there is a preferential distribution within the foetus itself, such that iron is directed first to blood cell production, leaving other developing foetal tissues such as the brain potentially vulnerable. For example, iron was diminished by 40% in the brains of infants born to diabetic mothers [1625067].

A number of studies have reported effects of maternal iron deficiency on maternal and infant cognition. As mentioned, the potential confounders in this situation include pregnancy conditions coexistant with iron deficiency, (e.g. diabetes [11085609, 16108452], prematurity or intra-uterine growth retardation).

Compared with iron replete mothers, 10 week old South African infants of mothers with iron deficiency anaemia had lower responsiveness, were developmentally delayed in hand-eye movement and overall quotient, and their mothers less maternal sensitivity during videotaped interaction [19158210, 15795446, 15671224]. Although the mothers did not differ in regard to postpartum emotion or cognition, one wonders whether their lesser responsiveness affected the baby or vice versa. (It is interesting that similar findings were reported of American mothers and their infants at 9-10 months of age [20431398]).

An American study found that the maternal iron deficiency was linked with the risk of schizophrenia in the offspring well into adult life - every fall of 1 g/dL in maternal haemoglobin was associate with a 27%

increase in the rate of adult schizophrenic spectrum disorder [18838630].

Some studies have been based directly on the newborn's iron status. In infants from Peru, lower cord iron status was associated with higher levels of negative emotionality and lower levels of alertness and soothability when tested as a neonate, across the full range of iron values, and this was not accounted for by sociodemographics or pregnancy history [15732057]. Amongst a sample of infants of diabetic mothers, those with low cord ferritin had neonatal EEG patterns that showed impaired auditory recognition memory, and subsequently had worse motor development at 1 year of age, compared to those with normal ferritin [15155871]. Follow-up at 3½ yrs showed persistent deficits in memory under high demand, with electrophysiological testing suggesting both encoding and retrieval processes were affected [20183732]. Israeli premature infants born before 34 weeks had significantly greater percentage of abnormal reflexes when tested at 37 weeks than those without iron deficiency [15318248]. There was evidence of the persistence of cognitive disadvantage in an American study that found an association between birth cord ferritin levels and a range of intelligence, language and motor skill scores when tested as 5 year olds. The results were quite marked - those in the lowest quartile of cord ferritin, compared with the median two quartiles, scored lower on every test, and were 4.8 times more likely to score poorly in fine-motor skills and 2.7 times more likely to have poor tractability [11865266].

Infancy

As background to the section of Table 1 on infancy, it should be noted that, although neonatal iron stores generally protect full term infants in the first months after birth, thereafter the infant is dependent on dietary intake at a time of rapid brain growth, so that the following 18 months are another period of particular vulnerability [17413089, 12536026]. There is some evidence that, even if not reflected in cord blood at birth, an infant born to an iron deficient mother is more likely to become iron deficient over the next 12 months than one born to an iron replete mother [10405849, 12219063]. Indeed, a Spanish study reported the risk of iron deficiency anaemia at 12 months to be 6.57 times higher, and this was not significantly altered when controlled for socioeconomic and feeding practices [2362876].

Elderly

Not shown in the Table, (because of the qualification in regard to studies on dementia discussed in the introduction), are three studies linking anaemia to risk of cognitive decline [16108938], dementia [15893409] and Alzheimer's disease [9141646]. A meta-analysis combining two of these studies found that the pooled hazard ratio for incident dementia in the presence of anaemia was 1.94 (95% CI: 1.32-2.87) [18691409].

Studies with specialised focus

Febrile convulsions have been associated with iron deficiency in some studies [15924837, 19229063], but not in all [19223207, 7782598]. If there is a causal link, the mechanism is unclear. In theory it could be related to some impact on immunity and the way infectious illness develops in these children, rather than any effect on brain physiology.

Breath holding spells are a common condition of early childhood, possibly due to immaturity of the developing autonomic nervous system, and have been observationally associated with iron deficiency, although by what exact mechanism this might work is far from clear [20464763, 12213607, 16278993, 16814080].

Depression has been linked with iron deficiency in pregnancy and post-partum mothers [19699836 , 15671224] as have emotional changes in their infants, children and adults [16040007, 10610080] (see individual studies listed in Table F1). Some have suggested this is evidence of iron's role in neurotransmitter function, for example the dopaminergic system [3653699].

Patients with *Tourette's syndrome* had lower iron status than normal controls, and this was associated with hypoplasia of the caudate and putamen on MRI imaging [16816233].

Attention deficit disorder patients had lower iron status in several studies and it has been hypothesised that this is more evidence of iron's role in dopamine metabolism [18279203, 18165896, 20453262]. Higher iron turnover was noted in one study of Egyptian patients with multiple sclerosis [18408021]. Lower levels were seen in several studies of patients with *autistic spectrum disorders* [11918106, 17109795, C453, 17352947] and in one open trial iron supplementation improved the autistic children's sleep [17352947]. In the latter two disorders, and less obviously also the first, the iron deficiency could clearly be the result of the disease (from disordered eating patterns), rather than the cause of it.

Impaired thermoregulation was associated with iron deficiency anaemia in two studies, in conjunction with elevated noradrenaline in once case and thyroid hormone changes in the other [6703092, 2239756]. Other studies have found higher noradrenaline excretion in iron deficiency, corrected by supplementation [2055611, 1127500], and it is possible that this is connected with cognitive impacts as a sign of autonomic dysregulation, particularly since other studies in iron deficient infants have found evidence of such autonomic dysegulation in alteration to respiratory-heart rate variability [11510439, C449, C450].

What do these studies tell us?

Collectively this substantial number of studies provides overwhelming evidence of an association between iron status and cognition in children, in both mental and motor development.

The associations have been found for tests of mental, motor, behavioural and emotional dimensions, including verbal skills, and emotional changes that could be described as increased fearfulness. There are also EEG changes, and evidence of impaired neurotransmission, including in relation to the special senses, that could be due to problems in myelination of the nerve tracts involved in these functions [16770951]. They are mainly seen with severe iron deficiency accompanied by anaemia, and associations that can be demonstrated many years after the initial finding of iron deficit.

It is noteworthy that these change are very much consistent with the effects of iron deficiency seen in animal studies, refered to earlier.

The degree of difference between normal and iron deficient subjects, particularly those with anaemia, is certainly great enough to be of clinical as well as statistical significance [16770951]. For example the reported decreases of from 6 to 15 points on the mental and from 6-17 points on the motor scales of the Bayley developmental index (e.g. see [6174719, 6834185, 3767413, 2472596, 2438635]).

The observational evidence provides a reasonable basis for a similar association in adults, but related to more subtle changes, such as detected in the EEG.

The crucial question is whether these associations are causal or incidental. This hinges on the potential for confounding. As with all such observational studies, there is considerable potential for confounding from factors coexisting with iron deficiency which themselves affect cognition [11930085]. This has been the subject of a lively debate on the specific question of iron and cognition for at least 20 years (e.g. [8369157, 2773839, 14132974, 11930085, C272, 19242028, 11160590]). Caution in interpretation is especially warranted in the studies where the proportion of variation in the cognitive variable that was due to the iron-related status was relatively small [11930085].

These confounding factors include poverty [17413089], other socio-demographic and environmental variables such as the amount of parent-child-interaction [19267294, 580855, 14132974], infection (particularly in developing countries, e.g. by malaria or worms [11744561, C368]), as well as coexisting imbalance of nutrients (e.g. zinc [19267294], vitamin D [3767413]) or excess of toxic elements (e.g. lead [18458574, 12520247, 11930085]). Those who are iron deficient may well be suffering from overall malnutrition, and a comprehensive picture of the subjects' nutrition status has not by any means always been provided in these studies. Such malnutrition could well account for many of the impacts reported in iron deficiency, including changes in temperament, the presence of a vulnerable period and persistence despite supplementation [2731496, 19605526, 15806897, 10828173]. It is important to realise that both developmental delay and generally poor nutrition are quite common in the type of populations amongst which many of the human studies described in this review were conducted [17697482, C272]. And we have discussed earlier in this review how the status of a number of the divalent cations (including manganese, cobalt, copper, zinc, cadmium, and lead) are interlinked because of their mutual reliance on a common transport mechanism (divalent metal transporter 1) across the gut wall [11930085].

This constellation of interrelationships is well illustrated by a 'case-control' study of primary school children from Jamaica, in which those who were failing in school had lower haemoglobin levels than the control children who were succeeding. But this was only one part of a group of risk factors which included being less likely to eat breakfast, having higher lead levels, impaired physical growth, more ill health, more hospital admittance for injury, less school attendance and - most likely the underlying cause of all of the above - poverty [C379]. Although school performance was still predicted by nutrition after controlling for socio-economic variables, there is only so much that statistical procedures can do to untangle such tightly interwoven negative influences on a child's cognitive performance.

The relationship between nutritional status, physical growth and neurocognitive development suggested in this study is another common possible confounder which can be very hard to separate out [17559332].

Another issue to consider is that iron deficiency could affect cognition either directly, for example through influence on neurotransmitter levels or myelination, or indirectly through influencing emotional responsiveness, which in turn could alter the way the child's parents relate to it, in such ways as to subsequently impair the nurturing that is so crucial to a child's cognitive development [9597172]. What one researcher nearly 50 years ago described as "a lack of `psychological' availability of the mother to the child" [14132974].

A crucial question that has occupied researchers for many years is to what extent anaemia, rather than any cause of anaemia such as iron deficiency, is responsible for cognitive deficits [17413089]. It is certainly possible to establish a direct correlation between haemoglobin and cognition. A meta-analysis incorporating five studies [1432416, 6840745, 1870641, C350, C366] calculated that each rise in Hb of 1 g/L was associated with a rise of 1.73 IQ points (95% CI: 1.04–2.41) [C364]. The studies we have to work from (as listed in Table F2) feature a confusing range of diagnostic criteria in regard to this question and this is summarised in Table F1. A significant proportion (around a fifth) were based on a diagnosis of anaemia without direct assessment of whether it was due to iron deficiency.

This question is of direct practical importance, because anaemia can be caused by things other than iron deficiency, particularly in the developing world. These include other nutrient deficiencies, lead poisoning, and infections (e.g. malaria or helminthic) [C368, 20433349]. For example, 73% of anaemic Pakistani children had normal total iron binding capacity (albeit that this is not the best measure of iron stores) [C354]. Even in a Western population, data from the US NHANES III survey that used much better tests for iron status showed that a diagnosis of anaemia had a sensitivity for iron deficiency varying from 15-30% and positive predictive value from 29-38% (depending on what Hb cut-off was used) [15687438]. These are not high numbers. On the other hand, in Chilean infants, some of whom had been iron supplemented at 6 months of age, 85% of the anaemic 12 month olds were iron deficient [17158425]. Obviously there is no single answer to this question, rather it will depend on the circumstance of each study. Ideally, since this review is concerned with the cognitive functions of iron, it would focus only on the direct cognitive impact of iron deficiency independent of anaemia. In reality, particularly for observational studies, such a luxury is not always practical.

Other limitations of this data set which are highlighted in Table F1 are the small subject numbers in many of the studies and the fact that less than a fifth of the studies were prospective. In regard to the cognitive testing methods used, although some tests, such as the Bayley developmental scales, were employed in a good number of the studies that were done on the applicable paediatric age group, there is a lack of consistency overall [18297894]. And there is some evidence that these scales are less helpful in children during their first 18 months of age than they are in those over that age [11160597, 11160596]. Some researchers feel that the more recent use of electrophysiological tests such as evoked potentials has been a big step forward in overcoming this methodological weakness [19022985], but such studies remain in the minority. The large majority of studies have been on children, far fewer on adolescents and adults (the subject number total for adults is dominated by a single study with n=28,834). More specific methodological issues concerning individual studies have been addressed elsewhere [11160596, C356].

Taking all this into account, it is the overall number, range of ages and circumstances of these studies, when combined with the fact that the large majority reported a significant adverse cognitive association, that gives good grounds for a strong suspicion that the link is causal - a suspicion that, however, only clinical trials can confirm!

A critical issue is at what level of iron deficiency is likely to cause adverse cognitive effects. This question has two elements. One is whether there is a dose-response effect, related to iron status, and if so at what level of lowered iron status cognitive impacts occur. The other is whether there is a step effect, related to the presence of anaemia and due to the specific pathophysiology of that condition, such as impaired oxygen delivery. Dose-response has been reported in some studies in regard to ferritin (e.g. [18410777]) and in others in regard to haemoglobin (e.g. [12074177], but only when there was concurrent iron deficiency). And whilst the majority of the adverse cognitive changes were seen in subjects from the developing world who

had fairly severe iron deficiency, a few were in ostensibly well nourished Western subjects with moderate iron lack. Overall, there is currently insufficient data to reach any definitive conclusion on this point.

In relation to a step effect from the specific pathophysiology of anaemia, observational studies provide only weak guidance, more so because the tests used for iron status in a number of these studies were relatively insensitive or, in some cases no direct tests of iron status were done at all [11160596, C355]. Moreover the studies give different answers to the question. For example, Table F1 shows a number reporting change in cognitive and other brain functions in subjects with iron depletion without anaemia. Whereas others that specifically looked for this did not find it [7322719, 6856400, 20335633]. (One could explain this by noting that some of those latter studies were conducted in 9-13 month old infants in whom the iron deficiency had probably not been present very long, a relevant consideration because anaemia is well along the path of the body's response to iron deficiency not only in severity but also in time [C355, C368]. But on the other hand, other data that did show this relationship were conducted in a similar age group [2472596]). And then there are several studies showing a gradient in effect, even if not strictly speaking a `dose-response', from normal iron through non-anaemic iron deficiency to anaemia in children [15318248, 18410777] and in adults [17344500].

Of all the questions to be answered, perhaps the most clinically important is whether correction of the iron deficiency will reverse the cognitive differences. This is likely to be determined by a combination of factors, including how severe, how long and in what relation to vulnerable periods the deficiency was [18297894]. From a neurodevelopmental perspective, foetal life and the first two years are obviously vulnerable periods. But one should not overlook the increasing evidence of the importance and vulnerability of adolescence for brain development [19699416], particularly since, with the combination of onset of menstruation, adoption of more personal dietary patterns, and the requirements of growth, this can also be a time of heightened risk for iron deficiency. Ultimately the answer to this question of reversibility and vulnerable periods should come from carefully conducted, adequately powered, controlled trials. But some help can be gleaned from prospective observational studies, particularly those in which it was possible to control or adjust to a reasonable degree for the important confounding factors such as poverty [16770951].

The studies of this type that we do have are summarised in the section in Table F1 labelled *Infancy with long term follow up*. Their results were far from reassuring. The longest data set currently available has cross-sectional observations from nearly two decades after what had been an initial trial of 3 months of iron supplementation given to 191 iron deficient infants in rural Costa Rica. Deficits held to be indicative of impairment of the dopamine system and the hippocampus were still seen 19 years later in those children whose iron deficiency was either severe initially or chronic [20406573, 19736288]. Cognitive test performance in some of that severe group declined by about 0.5 points per year (on a score with normal median value=100) [C452]. Findings also suggestive of long lasting dopamine-mediated neural processing came from a Chilean study in which children who had iron deficiency anaemia in infancy showed continued evidence through to 10 years of age of neurotransmission and sleep abnormalities [12538778, C366, 12441207, C454, C372]. And such ongoing cognitive deficits have not been restricted to lower socioeconomic groups or developing world countries. In the well-nourished, affluent population of Iceland, iron status at 1 year of age was associated with lower fine motor development scores on the child's 6th birthday [17407463]. They have been seen in the US and Israel.

At the same time, it should be noted that in all except two of these studies [17407463, 11865266], the affected children had severe iron deficiency and/or anaemia. And the studies did not fully account for the intervening iron status of the children, so that, even if they were iron replete at the end-point (which was not the case for all the studies), it is still possible that the ongoing deficits may have been partly due to iron deficiency continuing or recurring at some stage between the first and final measuring points.

Human clinical trials

There have been a considerable number of trials conducted in which iron has been given to subjects of various ages, and in which cognitive outcomes were measured. Supplements may have been oral inorganic iron (in some cases with vitamin C to boost absorption), intramuscular one-off or short course, fortification to infant formula or other food, or as part of a multi-nutrient combination. Over 100 publications were identified for this review - see appendix F1. In a number of cases this includes multiple papers published on a single trial. Whilst it is not always easy to know identify every such overlap, there appear to be around 79 separate trials on over 22,000 subjects summarised in **Table F3**. All but ten of these were in children and adolescents, none was specifically conducted with the elderly. Two thirds

showed at least one positive cognitive outcome, whilst there were three trials with significant negative outcomes.

Table F3: Characteristics of iron trials in Tables F4-F6 (N=77)

	% of studies	Subject n
Meta-analyses		
Included in meta-analyses	36%	6,618
Subject number		% with +'ve effect
<100	39%	67%
100-249	34%	78%
250-499	11%	70%
≥ 500	16%	55%
Age group		
Infants (to 2 yrs) *	51%	12,392
Pre-school children	10%	1,346
Primary school	9%	2,886
Adolescent	6%	703
Children (across wide age range)	10%	1,334
Adult (≥ 18 yrs)	13%	3,853
Elderly	-	-
	100%	22,514
Socioeconomic risk **		% of total n
Low	30%	13%
Intermediate	18%	17%
High	52%	70%
Cognitive outcome ***		
Some significant positive effect	65%	
No significant effect	31%	
Significant negative effect	4%	

As far as practical, each study has been counted only once (in relation to age, based on majority of subjects).
* includes one trial (n=333) of age range 6-36 months
** Socioeconomic risk is based on country of origin, not individual study sample circumstance
*** totals > 100% because some trials counted for both negative and NS outcomes

Not all of these trials were of such design and quality as to contribute a great deal to our understanding of how iron is involved in cognition. Some were not controlled, and hence were methodologically more like case reports or pre- and post-treatment observational studies. Sample sizes have mostly been small, (nearly three quarters involving under 250 subjects), particularly considering the amount of background `noise' that one might expect to find from confounding factors. Although many of those conducted in younger children used the Bayley scales of mental and psychomotor development, by no means did all trials use the same measures of cognition. Whilst in some the intervention lasted a full year, in others oral supplements were administered for what seems like a remarkable very short duration, (e.g. just days [2472596, 6174719, 6834185]), particularly given the poor absorption of inorganic iron, and the structural nature of the biochemical and anatomical defects that can be caused by iron deficiency, particularly during neurodevelopment.

Some data comes from trials in which iron was only one component of a supplement or intervention, creating the obvious difficulty of knowing which element of the intervention was biologically responsible for any cognitive effect. In addition there is the possibility in such trials of interactive effects. For example, a recent meta-analysis found that multinutrient supplements containing iron may increase the improvement in haemoglobin in some cases, and decrease it in others, compared to iron alone [18671894].

Overall it has therefore been impossible to combine the results of two thirds of these trials in any formal meta-analysis. The third that have allowed this appear in one or more of four separate published meta-analyses, and these are briefly summarised in **Table F4**.

Table F4: Clinical iron trials included in meta-analyses

PMID	Yr	Country	Age	Sample	n=	Groups	Dose	Durn	Tested	Cognitive measures	Out-come
Young children (< 2 yrs)											
7523647	1994	Canada	0–2 mo	From poor families	283	Fe vs regular formula	12.8 mg/l	15 mo	Every 3 mo from 6 mo	Bayley SID	+
14615726	2003	Canada	1 mo	Term infants	77	Fe vs pl	7.5 mg	5 mo	13 mo	Bayley SID	+
15321815	2004	Indonesia	6 mo	Commun. clinic, 40% anaemic	680	Fe vs Zn vs pl	10 mg	6 mo		Bayley SID	+
11192518	2000	Turkey	6 mo	Fe sufficient	24	Fe vs no Fe	1 mg/kg FS	3 mo		Bayley SID	NS
10451399	1999	UK	9 mo	Healthy term infants	493	Fe vs regular formula vs milk	1.2 mg/l	9 mo		Bayley SID	NS
338872	1978	USA	9–26 mo	Urban, IDA	24	Fe vs pl	5 mg/kg	x1		Bayley SID	+
2429622	1986	UK	17–19 mo	Urban, anaemic	110	Fe vs vit. C placebo	24 mg	2mo		DDST	+
2438638	1987	Costa Rica	12-23 mo	Urban ID/IDA/IR	191	Fe vs pl	IM as needed +	3 mo (oral)	4 mo post	Bayley SID	+
2472596	1989	Chile	12 mo	Urban, ID/IDA/IR	196	Fe vs pl Fe	45 mg	10 days 3 mo	10 d, 3 mo	Bayley SID	NS
6174719	1982	Guate-mala	6–24 mo	Urban IDA	64	Fe vs pl	5 mg/kg	1 wk		Bayley SID	NS
7678046	1993	Indonesia	12–18 mo	ID/IDA/IR	126	Fe vs pl	3 mg/kg	4 mo	4 mo post	Bayley SID	+
C363	?	Not known	6–24 mo	IDA	42	Fe vs pl	As needed	IM		Bayley SID	NS
Older children (> 2 yrs)											
11744561	2001	Zanzibar	6–59 mo	Anaemic (97%)	614	Fe vs pl (+/- worm Rx)	10 mg	12 mo		Language, motor score in severe anaemics	+
3701513	1986	USA	18–60 mo	Urban IDA vs IR	45	Fe vs pl	6mg /kg	6 mo		Bayley MDI/ Stanford Binet	NS
2773844	1989	Indonesia	5 years	Rural, ID/IDA/IR	139	Fe vs pl	50 mg	2 mo		Discrimination learning	+
2773845	1989	India	3 gps, 5-15 yrs	Urban, anaemic vs non-anaemic	170	Fe vs pl	30 or 40 mg	4-8 mo	Various	Various	+
16510631 16291354	2006 2005	Mexico	Ave 7 yrs	Urban, ID/IR lead exposed	602	Fe vs pl +/- Zn	30 mg	21 wk		Various IQ, cognitive, memory, hyperactivity	NS
2773846	1989	Thailand	9-11 yrs	School children ID/IDA/IR	1,358	Fe vs pl	4 mg/kg	16 wk		Non-verbal Intelligence, maths, Thai Language	NS

PMID	Yr	Country	Age	Sample	n=	Groups	Dose	Durn	Tested	Cognitive measures	Out-come
15333727	2004	Thailand	Ave 10 yrs	Rural school children, IR	397	Fe vs pl	300 mg FS 1x or 5x/wk	16 wk		Non-verbal Intelligence, maths, Thai Language	+
2773847	1989	Indonesia	6-18 yrs	Rural, a naemic vs non-anaemic	130	Fe vs pl	2 mg/kg	3 mo		Learning achievement	+
3836202/ 3836203	1985	India	6-18 yrs	Free meal recipi-ents, ID/IDA/IR	48	Fe vs pl	30/40 mg	8.5 wk		Memory tests	+
4072957/ 2857226	1985	Indonesia	6-18 yrs	Deprived rural area, IDA vs IR	119	Fe vs pl	2 mg/kg	13 wk		School achievement test scores	+
Adolescents											
3511017	1986	USA	14-24 yrs	Pregnant women, IR	38	Fe + vitamins vs only vitamins	60 mg	4 wk		Short term memory	+
8855856	1996	USA	Ave 16 yrs	Adolescent girls, ID	81	Fe vs pl	260 mg	8 wk		Verbal learning and memory	+
Adults											
15671224/ 15795446	2005	South Africa	18-30 yrs	New mothers, anaemic vs non-anaemic	81	Fe + vit.C/ folate or vitamins alone	125 mg	29 wk		Depression, stress, Raven's pro-gressive matrices	+
17344500	2007	USA	18-35 yrs women	ID/IDA/IR	149	Fe vs pl	60 mg	16 wk		Cognitive performance and speed	+
5448798	1970	UK	Women >20 Yrs	Anaemic women >20 Yrs,pre-menopausal	47	Fe vs pl	150 mg	8 wk		Psychomotor function	NS

Age at time intervention commenced
Dose: iron equivalent daily dose unless stated otherwise
Tested: refers to assessments done after intervention commenced (i.e. not baseline). If not stated otherwise, then tested at the end of intervention.
Outcome: + = significant difference in at least 1 cognitive/neurodevelopmental measure

Each meta-analysis had a different focus and will be considered in turn.

#1. Cochrane, 2001 11405989: looked at trials on children under 3 years of age with iron deficiency anaemia.

The trials included were published up to and including 1996, and were categorised based on whether the cognitive tests were undertaken in immediate proximity (5-11 days) to the treatment or not. Of the five trials on 180 children in which this was the case, four were able to be included in the actual meta-analysis, to yield a pooled difference in pre- to post- treatment change in Bayley Scale psychomotor development index (iron vs placebo) of -3.2 (95%CI: -7.24, 0.85) and in the mental development index of 0.55 (95% CI: -2.84, 1.75). The trials lasted 7 days, 10 days, 2 months and 4 months respectively. A further 2 trials on 160 children did not have contemporaneous cognitive testing.

Conclusion: "*There is no convincing evidence that iron treatment of young children with IDA has an effect on psychomotor development discernible within 5-11 days*".

Comment: The numbers of subjects were so small in relation to what is known about the variance of the measures used, it is entirely unsurprising that this data set did not produce any clear cut conclusion. For this reason the contribution of this meta-analysis to our understanding is limited, other than demonstrating how few trials at that time met the authors' stated criteria.

#2. Sachdev, 2005 15877905: looked at trials on children of any age, and was not restricted in regard to the subjects' baseline iron status. It included in its calculations 29 separate data sub-samples from 15 trials on 3,901 subjects, the most recent of which was published in 2005. (Four of those trials were also included in meta-analysis #1, and a further two had been reviewed but specifically excluded from it). Two trials involved iron supplementation for more than 6 months, the majority (other than those involving intramuscular injection) were for 2-4 months. The pooled estimate (random effects model) of the standardised mean difference in mental development score from iron supplementation was 0.30 (95% CI: 0.15-0.46, $p < 0.001$, with significant heterogeneity), whilst for motor development it was not significant (SMD= 0.09, 95% CI: -0.08-0.26).

The impact was most strongly seen for intelligence tests given to children over 7 years of age, in those who were anaemic or iron-deficient anaemic at baseline, and only in children at least 27 months of age. Evidence was not statistically significant for iron given in food or infant formula, or for less than 1 month. There was insufficient data to allow the authors to confidently differentiate therapeutic from preventive effects. The conclusions proved robust to a range of sensitivity analyses. Although there was significant heterogeneity, the authors believed they could account for this by explanatory variables such as baseline haemoglobin etc.

Conclusion: "*Iron supplementation improves mental development score modestly*".

Comment: The number of trials and subjects was substantially greater than meta-analysis #1, and hence allow a positive conclusion. However, in addressing questions such as the impact of non-anaemic iron deficiency the numbers in these categories were small.

#3. University of East Anglia group, 2010 20100340: was on trials in subjects of age $\geq$ 6 years, including adolescents and adults, without regard to baseline iron status. Fourteen such trials were included, involving 3,220 subjects (none including adult men), the most recent of which was published in 2007 (three were also in meta-analysis #2). All but three of the trials lasted 16 weeks or less.

Iron supplementation improved attention and concentration, irrespective of baseline iron status (standardised mean difference= 0.59, 95% CI: 0.29-0.90, without significant heterogeneity), and raised intelligence quotient by 2.5 points (95% CI: 1.24- 3.76) in anaemic subjects only.

Conclusion: "*There was some evidence that iron supplementation improved attention, concentration and IQ, but this requires confirmation with well-powered, blinded, independently funded RCTs of at least one year's duration in different age groups including children, adolescents, adults and older people, and across all levels of baseline iron status.*"

Comment: Although they did not find significant heterogeneity in their main finding, the type of subjects studied did vary considerably. The authors' cautionary note is therefore appropriate.

One of the most recent trials is worth singling out for its potential application in the Australian context. Women aged 18 to 35 years were categorised into three groups: iron deficiency with mild anaemia, iron deficiency without anaemia and iron replete. They were then randomised to receive either iron (60 mg elemental equivalent) or placebo for 4 months. The Detterman's Cognitive Abilities Test was used to assess cognition before and after supplementation. A significant improvement in serum ferritin was associated with a 5–7-fold improvement in cognitive performance, compared to improved speed in completing the cognitive tasks in those whose haemoglobin improved 17344500.

#4. Szajewska 2010 20410098: was on prevention trials, i.e. in non-anaemic, infants and young children in which baseline iron status was either demonstrated to be normal or who were considered "healthy". It included one trial in which the iron had been given to the child's mother during pregnancy. Six trials were included, involving 1,801 subjects, the most recent follow-up being published in 2008 (two were also in meta-analysis #2). The iron interventions lasted from 3-15 months.

Formally meta-analysing only the three trials that involved giving iron during early infancy (n=561), no benefit was found on Bayley mental development index at around 12 months of age, whilst a benefit at some stage was found for physical development index (WMD= 4.21; 95% CI: 2.31-6.12). Significant heterogeneity was not found in either case.

Conclusion: "*Limited available evidence suggests that iron supplementation in infants may positively influence children's psychomotor development, whereas it does not seem to alter their mental development or behavior.*"

Comment: This meta-analysis is useful in being the only one specifically focusing on preventative supplementation. Although they did not find statistically significant heterogeneity, the samples were by no means homogenous, since two of the trials were performed in Canada whilst the third was from Indonesia. The trials that did not get included in the formal meta-analysis showed little or no benefit, and the total number of subjects in the trials that were included was modest. This paper therefore offers only weak evidence that preventative iron supplementation helps cognition.

Trials not included in the meta-analyses

Table F5 shows trials not included in the above four meta-analyses, because they were more recent, or for some other reason. **Table F6** lists trials not included in the meta-analyses in which iron was only one component of a multi-nutrient mix.

An interesting finding was that seen in an Indonesian follow-up at around 11 years of age of children who had been given iron for a 3 month period during their first 5 years of life. Although the iron was part of a multinutrient supplement and hence the relevance to iron less certain, it was noteworthy that those who were treated before 18 months of age showed persistent improvements in cognitive test scores, whereas those who had received their first iron after that age did not 9394687. This adds weight to the notion of a critical period for correction of nutritionally caused cognitive effects.

Table F5: Clinical iron trials not included in meta-analyses

PMID	Yr	Country	Sample/age	Group(s)	n=	Iron Rx	Dose	Durn	Tested	Cognitive measure	Out-come
Young children (< 2 yrs)											
19158210	2009	South Africa	6-8/52 pp	IDA vs IR	95	Fe vs pl	125 mg FS	26 wk	9 mo	Mother-child interactions	+
17766527	2007	Germany	Premature babies	14 vs 61 d pp	164	Enteral Fe	2-4 mg/kg		5.3 yrs	Cogn scores	NS
15499963	2004	Turkey	6 mo	ID/IDA vs IR, single blind	108			3 mo		Denver + Bayley SID	+
15447897	2004	Bangladesh	6 mo	At risk (2/3rds mild anaemia	221	Fe vs other nutrients	20 mg	6 mo		Motor development, orientation-engagement.	+
14523176	2003	Chile	6 mo	No IDA	1,657	High vs low intake		6 mo		Information processing, affect, tremor	+
C360	1996	Chile	6 mo	Healthy, IR	944	Fe vs normal		6 mo		Bayley SID	NS
11487753	2001	Canada	LBW	LBW	58	Low vs high Fe formula	13.4 vs 21 mg/L		3,6,8, 12 mo	Griffith's Development Assessment	NS
11419674	2001	Turkey	Infants	IDA	20	Fe , uncontr		12 wk		VEP	+
C333	1985	Greece	3-25 mo	ID/IDA	48	Fe , uncontr	50 mg IM	x1	10 d, 20 d	Bayley SID	+
10902991	2000	Indonesia	12 mo, 18 mo	At-risk	136	Fe +/- energy vs control	12 mg	12 mo		Bayley SID, walking age, social, emotional	+
6834185	1983	Chile	15 mo	Urban	37	ID/IDA/IR	3-4 mg/kg	11 d		Bayley SID	+
6856400	1983	USA	9-12 mo	Urban	38	ID/IR		IM	7 d	Bayley SID	+
C349	1997	Portugal	9 mo		15	Fe, uncontr		3 mo		Griffith's Dev.Assesst.	+
8804327	1996	Costa Rica	12-23 mo	Low middle class	86	ID/IDA/IR	6 mg/kg	6 mo	3 mo, 6 mo	Bayley SID	NS
10088991	1999	Guatemala	12-24 mo	IDA	132	Fe, uncontr	5 mg/kg	2-3 mo		Bayley SID, behaviour rating	NS
15526591	2004	Bosnia	6-24 mo	Anaemia vs non-anaemia	120	Fe, uncontr				Bayley SID	NS
2773841	1989	PNG	1 yr	+/- malaria	96	Fe vs pl	IM injection	1x		Attention	+

PMID	Yr	Country	Sample/age	Group(s)	n=	Iron Rx	Dose	Durn	Tested	Cognitive measure	Out-come
Older children (> 2 yrs)											
15226754	2004	Greece	3-4 yrs	IDA	49	Fe vs pl	15 mg	2 mo		Cogn: errors of commission, specifi-city, accuracy	+
3962908	1986	Guatemala	3-6 yrs	IDA vs IR	50	Fe, uncontr	3 mg	12 wk		Discrimination	+
C440	1988	China	Children	IDA	130					Attention, learning	+
C438	1989	China	6-36 mo	IDA	333	Fe fortified jam, uncontr		3 mo		Developmental quotient	+
9774808	1998	Peru	Pre-school	At risk	108	Fe in biscuits		6-8 wk		Goodenough-Harris Test, Wechsler IQ	+
16685054 17967217	2006 2008	Australia	Pregnant women	Offspring	262	Fe vs pl	20 mg	To term	4 yrs 8 yrs	IQ Behavior score	NS -
18571983/ 15351367	2008 2004	Mexico	8-10 yrs	ID	20	Fe	To repletion			Working memory and ERP	+
14723316	2003	India	Ave 9.3 yrs	Anaemia	52	ID vs control				IQ, auditory ERP	+
C275	1987	India	8-15 yr	Underprivi-leged	130	Fe vs pl	60 mg	60 d x2/y	4,8,12 mo	Digit span, maze test, visual memory test, and clerical task scores	+
Adolescents											
19634512	2009	India	Adolescents	ID/IDA/IR	120	IR :Fe vs pl ID/IDA: Fe	600 mg/wk	8 mo	4/12, End	Cognitive and scholastic performance test scores	+: all gps
C249	1998	Northern Ireland	12-15 yr	ID vs replete (post-hoc)	413	Fe vs pl	17 mg	16 wk		IQ	+
Adults											
19474138	2009	USA	Female solidiers		219	Fe vs pl	100 mg FeS	8 wk		Mood: vigor score	+
18574611	2008	Egypt	Young adults (ave 22 yr)	IDA	28	Fe, uncontr	195 mg	3 mo		Wechsler memory and IQ, ERP, EEG	+
18423335	2008	Turkey	Adults	IDA	51	Fe, uncontr		3 mo		P300 and EEG power spectra	+
C322	1991	USA	18-40 yr women	ID	34	Fe vs pl		8 wk		Short term memory	+
5338945	1966	Wales	15-65 yr women	Anaemia vs non-anaemia	89	Fe vs pl	200 mg	8 wk		Subjective lack of concentration, tiredness	NS

Footnotes same as Table 4

Table F6: Clinical trials not included in meta-analyses in which iron was one component of multi-nutrient supplementation

PMID	Yr	Country	Sample/age	Group(s)	n=	Iron Rx	Dose	Durn	Tested at	Cognitive measure	Outcome
Young children (< 2 yrs)											
20484548	2010	Nepal	1-36 mo	High proportion of	3,264	Fe + folic	12.5 mg	1 yr	3 mo'ly	Walking: age, delay	NS. -
C180/C181	2007		4-16 mo	ID/IDA	569	vs pl *			39 & 52 wk	Delay in walking	NS
19322104	2009	Nepal	4-17 mo		567				x5	Executive function	+
		Zanzibar	5-18 mo		877				2 monthly	Night and total sleep durn	+
16920865	2006	Zanzibar	5-11 mo	At risk	354					Age at walking	+
10074011	1999	UK	Infants (ave 7.8 mo)	Inner urban	100	Fe + multinutr vs unfortified	1.2 mg/100 ml formula	to 18 mo	18, 24 mo	Griffith's Dev.Assesst.	+
16280435	2005	South Africa	6-12 mo	At risk rural	361	Fe + multinutr vs unfortified porridge	11 mg/40 g dry product	6 mo		Motor milestones	+
18326610	2008	Bangladesh	Pregnant women	Offspring	2,853	Fe + folate vs Fe + multinutr	60 mg	To term	7 mo	Problem-solving	+ **
										Bayley motor	NS
9394687	1997	Indonesia	18-60 mo	Rural	158	Fe + multinutr		3 mo	11-12 yrs	Working memory	NS
			6-17 mo		73						+
10902992/	2000	Indonesia	12-18 mo	Rural anaemic +	38	Fe + multinutr	12 mg	6 mo	2, 4, 6 mo	Play behav, walking age	NS
10902988			rural	control						Bayley motor,	+
10902994					36					Bayley mental, interaction	NS
Older children (> 2 yrs)											
18541560	2008	Thailand	5-13 yrs	School children	569	Fe + Zn + Iodine + vit.A	5 mg	31 wk		Visual recall	+
10075336	1999	South Africa	6-11 yrs	School children	115	Fe + Iodine + vit.A vs pl	Fortified biscuits	43 wk		Digit span memory	+
12907410	2003	South Africa	6-12 mo	At risk urban		Fe + multinutr vs control	Compli-ment.food	6 mo		Psychomotor develop-ment	NS
19242031	2009	India	9-13 yrs	Municipal schools	161	Fe + folic	100 mg, 1x or 2x/wk	1 yr		Digit span and other memory clerical task	+
7115656	1982	India	5-8 yr	At risk	122	Fe + folic vs no Rx(n=94), vs pl (n=28)	20 mg	60 d		Indian adapted IQ test	+

PMID	Yr	Country	Sample/age	Group(s)	n=	Iron Rx	Dose	Durn	Tested at	Cognitive measure	Outcome
Adolescents											
8031738	1994	UK	13-14 yrs	Adolescents	51	Fe + multinutr	12 mg	16 wk		Verbal and non-verbal intelligence	NS

Footnotes same as Table 4, in addition:

Multi-nutrient classification based on the active intervention, does not include studies comparing multi-nutrient with iron vs multinutrient without iron, or added Vit.C alone.
* Rx groups in some of Nepalese data sets were post-hoc found not to be matched in regard to relevant potentially confounding variables
** Randomisation was to timing of supplem, not Fe vs other. + = a small diff. in one problem solving test for infants of low BMI mothers only

Trials with specialised focus

Breath holding spells: Several trials have demonstrated that iron therapy is effective in reducing the incidence of these attacks [10451402, 5823631, 9108851], two of which have been combined into a formal Cochrane meta-analysis [20464763].

Attention deficit disorder symptoms have improved after iron supplementation in several clinical trials and case reports [18054688, 9246217, 16263988].

Unexplained fatigue is also associated with iron deficiency [11190004] and was corrected by iron supplementation in a Swiss trial of 144 adult women [12763985]. Most recently this was seen, along with improvements in general mental health and vitality, in a trial of 66 Australian women, occurring to equal extent whether the iron was given as oral supplementation or via a diet high in bioavailable iron [11506061]. It must be said that treating fatigue with iron supplementation is not new - it has a long tradition in clinical medicine, and trials attempting to demonstrate its efficacy (with variable success) date back more than 50 years [13800263, 5448798, 5650686, 5338945]. Whether such fatigue is related to CNS function, given its unexplained nature, is open to discussion. It should be noted that iron deficiency can definitely cause decreased capacity to do physical work and increased fatigue in connection with such work, and that this also is improved by iron therapy [12540406, 9988823, 8147338, 868783].

Some trials, whilst they may offer less `pure' evidence on the role of iron specifically, have addressed the more complex holistic situations in which iron deficiency is often found in the developing world. For example, trials in which iron supplements were given together with treatment for worm infestation, with benefits seen on cognitive outcomes [8492277, 11732150, C230]. In others, iron was given with other nutrients, such as zinc, which gives rise to uncertainty as to interactive effects on the effectiveness of the iron, which some trials have shown whilst others have not [11694609, 16002793].

Prevention trials

An important public health perspective is provided by trials that were preventative in intent, i.e. iron supplements were given to subjects without regard to their initial iron status, such as the ones in meta-analysis #4. In practice, some of these were closer to the ideal of preventative, i.e. they were conducted in subjects with a low risk of having serious iron deficiency, whilst others were in groups with such high underlying deficiency prevalence that they were close to being therapeutic trials. Table F7 shows the summary breakdown.

Table F7: Iron prevention trials with cognitive outcomes (N=21)

Risk	N	n	References
Low risk			
Children	5	839	10451399, C349, 10074011, 14615726, 7523647, 3511017, 16685054, 19474138
Adults	3	559	3511017, 16685054, 19474138
+'ve	75%		
Intermediate risk			
Children	3	2,625	C360, 14523176, 11192518
Adults	0		
+'ve	33%		
…			
Children	10	2,961	11744561, 2773841, 15321815, 15447897, 16920865, 16280435, 15333727, 9774808, C275, C360, 14523176, 11192518, 12907410
Adults	0		
+'ve	100%		
+'ve	76%		

Trials in which iron/Hb status was not considered in sample selection. Does not include trials in which only one arm of the trial was on non iron-deficient subjects
Risk category is based on country and sample group
+'ve = significant improvement in at least one cognitive outcome as % of trials in that risk category
NB: two high risk and one low risk children's trial involved iron as part of multi-nutrient supplementation

What do these trials tell us?

Once again it is necessary to consider confounding and other methodological limitations when assessing what conclusions can be drawn from what seems to be a substantial number of clinical trials.

In giving iron supplements to deficient subjects, there is likely to be an impact on aspects of health quite separate from the brain, which nevertheless can themselves influence cognitive and developmental outcome. One such factor is immune function. To the extent that correction of iron deficiency and anaemia lowers rates of infection, diarrhoea and other illness, such benefits are certainly likely to positively affect a child's development and learning [16413877, 16413878], including by influencing how much sleep they get [8795841]. At the same time, it should be acknowledged that such effects are by no means straightforward or one way. For example, there is a lively debate on whether iron deficiency offers protection against malaria and other infections or not [19588399, 19285567, 19022986, 18297896] (and indeed whether iron should wisely be given in endemic malaria areas where there are inadequate medical facilities to treat it[18297895]).

Another potential confounding factor is the effect of iron on physical growth and the effect of that growth on psychomotor development - the kind of development that some have concluded is more likely to show benefit from iron supplementation in infancy than is mental development [20410098, 19322104]. As one of the leading experts in this field put it: "*psychobiological development changes are not necessarily caused by brain changes; there are other mechanisms that also affect development (e.g., biomechanics)*" [11160597]. At the same time, there has been a notable lack of consistency in the reported effects of iron supplementation on physical growth [17158406], with some trials suggesting there could be an adverse effect [7910275], whilst others showed just the opposite [2134529]. This mixed picture has been highlighted by a meta-analysis on this question [17010257].

Taking this all into account, it is nevertheless true that the volume of clinical trial evidence is considerable and has been steadily growing.

Thus a detailed and often-cited individual review found 33 intervention trials (and 10 observational studies) published up to 2000. It concluded that: "*in anemic children, <2 y old, short-term trials of iron treatment have generally failed to benefit development. Most longer trials lacked randomized placebo groups and failed to produce benefits.... It therefore remains uncertain whether the poor development of iron-deficient infants is due to poor social backgrounds or irreversible damage or is remediable with iron treatment. Similarly, the few preventive trials have had design problems or produced no or questionable benefits only. For children >2 y old, the evidence from RCT is reasonably convincing but not conclusive*" 11160596. The authors also pointed out that most of the studies lacked statistical power due to low sample sizes, and had durations of treatment and follow-up that were very short in relation to the longitudinal development of cognition in children.

That review was presented at a meeting in May 2000 of many of the world's leading experts on iron deficiency and cognition. In the discussion that followed the presentation, one of them commented: "*it is very sobering. I have been working on iron deficiency for 25 years now, and really trying to do good studies. After all this effort, we still cannot give definite answers.*" 11160596.

Since this review, a further 31 trials have been published, three quarters of which had at least one positive cognitive result. Taking these into consideration, along with the formal meta-analyses summarised earlier, does allow us to reach conclusions somewhat stronger than the above quotation. It now seems clear that properly timed iron repletion does produce significant cognitive benefits.

Looking at the extent of the cognitive improvements seen after iron supplementation, in many cases these were modest in comparison with the level of differences reported in many of the observational studies, representing in some cases only 1-2 weeks of difference in development 11160596. This might add some weight to the notion that the deficits of iron deficiency may not be fully reversible. On the other hand, these are levels of difference similar to those seen for other insults to development, whether they be from nutritional or other causes 11160596. And the degree of improvements reported from some of the trials was really rather startling. For example, the 5- to 7-fold improvement in cognitive performance seen in American women with relatively mild iron deficiency 17344500.

The iron supplementation trials do not definitively resolve the question of what level of iron deficiency is likely to bring about cognitive changes. Although the evidence is definitely stronger for positive outcomes in subjects with severe iron deficiency anaemia, this reflects the type of subjects studied in the majority of the trials that have been conducted. But it is also the case that some of the trials found significant improvement with supplementation of non-anaemic, iron deficient subjects, despite the lack of any cognitive association at baseline 6834185, 2472596. Whilst meta-analysis #1 specifically excluded trials in non-anaemic subjects, #2 and #3 looked at this sub-group and neither found significant effects. The relevant statistics from meta-analysis #2 are shown in Table F8. Whether this is because the studies were collectively not methodologically capable of detecting such an effect, or because there is no such effect, can only be guessed.

Table F8: Sensitivity analyses from meta-analysis #2 in relation to iron and anaemia 15877905

	N	**SMD** (95% CI)	p value	Heterogeneity
Hb				
< 11 g/dl	14	0.49 (0.23-0.74)	< 0.001	39.82 (p<0.001)
> 11 g/dl	13	0.14 (-0.06-0.34)	0.181	31.43 (p=0.002)
Deficient, anaemic	11	0.50 (0.25-0.75)	< 0.001	21.57 (p=0.017)
Deficient, non-anaemic	4	-0.11 (-0.36-0.14)	0.386	2.12 (p=0.548)
Deficient ± anaemic	15	0.31 (0.06-0.56)	0.014	41.34 (p<0.001)
Replete	8	0.33 (0.11-0.55)	0.003	11.40 (p=0.122)

N of analytic components (essentially equivalent to data sets)
SMD standardised mean difference for mental development score

Another perspective on this issue comes from the prevention trials summarised in Table F7, particularly those in 'healthy' children from populations at low risk of underlying iron deficiency. Although the number of trials in some of the categories was not large, they provide an encouraging public health message - that routine efforts to improve iron status within the general community is likely to lead to significant gains in cognitive outcome, and this applies to both developing and developed countries.

Regarding the question of irreversibility of cognitive impact from iron deficiency despite supplementation, a few trials have looked at longer term follow-up 16770951, but none have involved longer term treatment. In most cases it seems that supplement regimens were based on the criterion of a one-time restoration of iron stores. Whilst this may be practical and a way to minimise the risk of iron toxicity, it is a weakness of the current data that conclusions about long term damage are not based on a solid set of trials that aimed to ensure long term maintenance of adequate iron. Particularly since the environmental and socio-economic conditions in which most of these long term subjects live were unlikely to improve during their childhood.

On the other hand, animal studies and research on other neurodevelopmental insults does support the notion that, when the cognitive damage occurs during critical periods, it may not be repaired when the insult is removed. Despite the plasticity of the human brain, there are good reasons to believe this could be true in relation to the known effects of iron deficiency on myelination and neurotransmitter regulation, including the more recent evidence from human EEG and evoked potential studies 16770951, 18297894.

Conclusion

Based on what is known already it is questionable whether, for ethical reasons, there are likely to be many more placebo controlled, clinical trials on severely iron deficient or iron deficient anaemic subjects 11160596. What we may see are more prevention trials, trials on subjects with mild to borderline iron deficiency, trials comparing different iron interventions, and trials using more sophisticated cognitive tests targeted at the presumptive neuropathology of iron deficiency (such as impaired myelination, dopamine, γ-aminobutyric acid, and serotonin neurotransmitters).

At this point in time, we can conclude that, whilst the potential for confounding is substantial, there is very strong evidence that iron deficiency adversely affects human cognition, that these deficits respond to iron repletion but not always to the full extent, and that both of these facts are particularly so when the deficiency is severe, persistent, or occurs during vulnerable neurodevelopmental periods such as foetal life or early childhood.

There is insufficient evidence to determine whether, apart from being a sign of such persistence and severity, anaemia has of itself specific adverse cognitive impact. The evidence on whether that there are adverse cognitive effects from non-anaemic iron deficiency of mild degree, in people without significant socioeconomic deprivation (for example otherwise healthy young adults in the US or Australia), and that

such effects are correctable with iron repletion, is suggestive but by no means convincing.

Appendix F1: Human trials of iron supplementation with cognitive/developmental outcomes

Pregnant women

3511017 Groner JA. et al. A randomized trial of oral iron on tests of short-term memory and attention span in young pregnant women. J Adolesc Health Care. 1986 Jan;7(1):44-8.

Maternal and infant combined

17967217 Parsons AG. et al. Effect of iron supplementation during pregnancy on the behaviour of children at early school age: long-term follow-up of a randomised controlled trial. Br J Nutr. 2008 May;99(5):1133-9.

16685054 Zhou SJ. et al. Effect of iron supplementation during pregnancy on the intelligence quotient and behavior of children at 4 y of age: long-term follow-up of a randomized controlled trial. Am J Clin Nutr. 2006 May;83(5):1112-7.

15671224 Beard JL. et al. Maternal iron deficiency anemia affects postpartum emotions and cognition. J Nutr. 2005 Feb;135(2):267-72.

15795446 Perez EM. et al. Mother-infant interactions and infant development are altered by maternal iron deficiency anemia. J Nutr. 2005 Apr;135(4):850-5.

3993612 Adair LS. et al. Outcome of maternal nutritional supplementation: a comprehensive review of the Bacon Chow study. Am J Clin Nutr. 1985 May;41(5):948-78.

Premature or light for gestational age infants

17766527 Steinmacher J. et al. Randomized trial of early versus late enteral iron supplementation in infants with a birth weight of less than 1301 grams: neurocognitive development at 5.3 years' corrected age. Pediatrics. 2007 Sep;120(3):538-46.

15520109 Ohls RK. et al. Neurodevelopmental outcome and growth at 18 to 22 months' corrected age in extremely low birth weight infants treated with early erythropoietin and iron. Pediatrics. 2004 Nov;114(5):1287-91.

11487753 Friel JK. et al. A randomized trial of two levels of iron supplementation and developmental outcome in low birth weight infants. J Pediatr. 2001 Aug;139(2):254-60.

C437 Bender-Gotze CH. et al. [Effect of iron-supplemented baby milk on iron balance and neurological development of premature and full-term babies in their first year of life]. Monatsschr Kinderheilkd 1985;133:616.

Children and adolescents

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Chapter xx: Other B vitamins

Executive summary

Thiamine is required for several enzymes involved in energy production, and has known deficiency states that include dementia, for example in association with alcohol excess. The evidence for thiamine supplementation affecting cognition outside of these syndromes is weak.

Choline is a methyl contributor to one-cycle metabolism closely linked with the action of folate. It plays a vital role in the synthesis of cell membranes, particularly phosphatidylcholine and sphingomyelin, both of which are basic components of neuronal cells. Converted to acetyl-choline, it is an important neurotransmitter in its own right. In animal studies, choline sufficiency during pregnancy and to a lesser extent post-natally has a direct influence on the infant's memory and cognitive capacity on an apparently permanent basis. There is no convincing evidence as yet that this translates into human terms. However, a number of trials of choline and its precursors have had modest positive results in improving cognition in Alzheimer's disease. It also shows some promise as a neuroprotectant agent.

Niacin is another water soluble B vitamin that has a role in energy production and is converted to an intra-cellular signalling compound that is involved in neural plasticity. It also has a classical deficiency state (pellegra) which features dementia. However, there is little evidence of any application of niacin supplementation to enhance cognition.

Thiamine

Thiamine is a co-factor in over two dozen enzymes, but most notable is its function in three that are involved in carbohydrate metabolism, including the production of energy from glucose in the Krebs cycle [15303623]. Approximately 30% of brain glucose is fully processed through this cycle. Hence, as brain is one of the most demanding organs for energy production from glucose, it has amongst the highest concentrations of thiamine (along with skeletal muscle, liver and kidneys) [11899071]. There is a specialised transport mechanism for thiamine across the blood-brain barrier and into neuronal cells, but this is relatively easily saturated [17645457, 9719389].

When aerobic metabolism is impaired, mitochondrial dysfunction and oxidative stress result, along with some degree of lactic acidosis and alteration of other `downstream' enzymes and compounds, including those needed for amino acid metabolism, production of nucleic acids, neurotransmitters (including glutamatergic), fatty acids and steroid hormones. All of this is seen in experimental thiamine deficiency. In addition, thiamine also has a much less researched structural function within the nervous system in relation to membrane structure and function [20932820, 20850489, 18642074, 17685850, 16527765, 15337301, 15303623, 12611562, 11850106]. Thiamine also seems to play a role in protein processing, peroxisomal function, and gene expression [17685850]. It may be involved in some way in cholinergic and serotonergic pathways [15997211, 8239567, 7044229, 15164618].

These general and specific functions may help explain why, in animal experiments of thiamine deficiency, both non-specific and specific damage is seen. The overall effect is to induce apoptosis and neurodegeneration [18642074]. Inflammation is also a feature, possibly due to activation of microglia [20932820], and a progressive encephalopathy results [20674425]. So, for example, impaired neurogenesis was observed in the hippocampus of thiamine deficient mice, along with decreased transketolase activity [19686241, 17936635], which is consistent with the experimental evidence of memory deficiency as a sign of this deficiency [15997211].

Thiamine is a water-soluble vitamin with relatively limited storage within the body [15522161, 9719389]. Deficiency can be precipitated by liver failure or excess diuretics, or by conditions which substantially raise metabolic energy demand, for example burns, severe trauma, hypermetabolic malignancy [19501976, 19067139, 17673878, 11127971, 10758842]. Long term use of certain drugs, such as some antibiotics and anti-convulsants, can compromise thiamine status [12611562]. Thiamine deficiency is certainly not uncommon, although rate in children from the developed world [16091511], but much often seen in the elderly, in whom there is evidence of diminishing thiamine status in the brain with normal aging [8522961], [16987159]. Amongst 30 geriatric outpatients in the US, 57% had thiamine status below the reference range for healthy adults (although this was based on an now out-of-date biological assay) [8935438]. Slightly less (50%) of a sample of community living elderly Canadians had marginal status, and of 118 consecutive hospitalised in-patients in a geriatric ward in Belgium, 39% had marginal and 5% severe thiamine deficiency (both studies used the current standard of enzyme activation assay) [8157855, 9933732]. Amongst patients admitted to an Australian palliative care unit, the proportions were 28% and 36% respectively [7529104]. In patients admitted to an Irish acute geriatric ward, symptoms of delerium were seen twice as commonly in those with thiamine deficiency than in those without [8034199]. Much more vague was the finding from a French case-control study, in whom thiamine status was significantly reduced in patients diagnosed with “neurosis” compared with controls [970836].

The classical clinical syndrome of thiamine deficiency is beriberi, in the so-called ‘dry’ form of which neurological symptoms are predominant, which can include paraesthesiae, loss of motor and coordination function, pain, nystagmus and mental confusion [12611562, 11899071]. The other classical picture of thiamine deficiency is that associated with alcoholism, both acutely (Wernicke’s encephalopathy, the standard signs of which are confusion, ataxia and opthalmoplegia) and as a chronic dementing disorder (Korsakoff’s psychosis, featuring memory loss and behavioural disturbance) [15303623]. (There is some potential confusion in terminology, in that collectively the syndrome of alcoholic brain disease is often called Wernicke-Korsakoff syndrome [14974055], moreover these terms may also be used to describe acute and chronic thiamine deficient neuropathology regardless of its cause). Different individuals appear to have differing sensitivity to alcoholic neuropathology, which may be related to genetic variations affecting the transketolase enzyme [10466187], as indeed do different regions of the brain. The more susceptible structures include the cerebellum (perhaps the most sensitive), mamillary bodies, thalamus, hypothalamus, and brain stem [16527765, 15303623]. Post-mortum analysis suggests that such thiamine-deficiency brain damage is often not diagnosed during the patient’s life [11304071, 11198705].

Thiamine is clearly the treatment of choice, indeed urgency, in Wernicke’s encephalopathy. It may be given

with other B vitamins, (such as B , pantothenate and riboflavin), because of the possibility that these are also directly affected by alcoholism and involved in the brain damage, or because of `downstream' effects of thiamine deficiency referred to above [9719389]. In established alcoholic dementia, cognitive benefit is much less likely (although this is surprisingly poorly documented in proper clinical trials) and hence preventive adminstration of thiamine to alcoholics has been recommended by some [16117048, 12578229, 10758842, 9719389]. However, a Cochrane meta-analysis in 2004 found no evidence to support such preventive supplementation [14974055].

Several trials have looked at the impact of thiamine supplements in subjects whose thiamine status was either normal or sub-optimal (in some cases this was presumed, and in others documented). Oral supplements given to 120 healthy young women for two months resulted in an increase in reaction time and subjectively reported `clear headedness', compared to placebo in a Welsh trial [9122365]. Thiamine supplementation was given to 76 elderly subjects with marginal baseline status in a New Zealand trial. Whilst there was significant improvement in an overall quality of life sub-score, there was no such change in cognitive measures, although the authors commented that this may have been because the baseline level of cognitive impairment was negligible [9322569]. A mixture of intravenous vitamins B and C given to patients hospitalised for fractured femur improved thiamine status, but did not improve their mental state [3364308].

Because it is clearly relevant to dementing symptoms in chronic alcoholism, there has been interest in whether thiamine is involved in other dementing disorders, particularly Alzheimer's disease. A number of observational studies have reported lower plasma and brain levels of thiamine in these patients [8619543, 8815392, 1477827, 2087217, 3395256], some of which involved comparison with non-Alzheimer's demented or Parkinson's disease controls [9349545, 9570639, 7487560]. A few small trials of thiamine supplementation have been conducted, all of which found at least some improvement in cognitive status [8815393, 8251051, 1986730, 2969232]. However, a Cochrane review in 2001 combining three of these trials (totalling 44 subjects completing the trials) found these results inadequate to undertake any meta-analysis or reach any clinical conclusion [11405995]. Another systematic review found the evidence for this "weak" [17628125].

A very small uncontrolled trial of thiamine in autism reported benefits [12195231].

Choline

Choline is a water-soluble vitamin generally included within the B group. Like folate, it is a methyl donor, consisting as it does of three such groups. It feeds into the one-carbon metabolic pathways already considered in the previous chapter through being converted to betaine, which (as shown in figure H1) is required in the B -dependent step from Hcy to methionine. Choline deficiency can therefore cause

hyperhomocysteinaemia [12] [18716669, 17212955, 16600945, 15699233, 15941891]. Choline plays a vital role in the synthesis of cell membranes, particularly phosphatidylcholine (also known as lecithin - a popular lay supplement) and sphingomyelin, both of which are basic components of neuronal cells. These membranes provide neurones with the physicochemical properties essential to transmission of signals along the axons and dendrites. Converted to acetyl-choline, it is a neurotransmitter in its own right, with cholinergic pathways being involved in many parts of the nervous system, including the autonomic and memory functions [15611726, 14747511]. There is a specific high affinity mechanism to take choline from the extra-cellular space into the presynaptic terminals [15611726]. Although choline can be synthesised within the body, it is now considered an essential nutrient, and is obtained from foods which contain cell membranes, and is especially rich in eggs and organ meats [18716669, 17212955]. Citicoline is choline precursor and is a popular lay supplement [19122569].

Because clinical diagnosis of choline deficiency is rare outside of the artificial environment of total parenteral nutrition, the impact of choline on neurodevelopment and cognition has been largely studied in animal experiments. In pregnancy choline is selectively concentrated across the placenta to the foetus, and choline deficiency can cause neural tube defects similar to that seen with folate, not surprising considering its close link with that vitamin in one-carbon metabolism. In later pregnancy, choline is essential for normal development of the hippocampus and of memory and other forms of long-term potentiation. As was the case with the Hcy nutrients, choline deficiency can impact genotypic expression [18716669, 17212955]. Choline supplementation given to animals during pregnancy results in improved cognitive performance in the offspring, including life-long memory enhancement, to such an extent that some researchers have talked about “metabolic imprinting”, probably involving the cholinergic synapses and in the hippocampus, through enhanced DNA methylation, altered gene expression, and associated changes in stem cell proliferation and differentiation [18793620, 18778697, 18323570, 17212955, 15640516, 14715695, 14645379, 12946691, 11023003]. The same is seen to some extent post-natally, including in aged mice subjected to artificial memory impairment [12946691, 3378679, 2860578]. The question is to what extent these animal findings are applicable to humans. In theory at least, the amount of acetyl-choline released at the cholinergic symapse is susceptible to external enhancement, including by dietary change [6867732]. There is no data in any way replicating the animal findings of ‘metabolic imprinting’. Indeed, the only analagous study was one looking at relationships between maternal and cord choline levels at birth, and the child’s IQ at 5 years of age - there was no correlation [18400712]. There were no consistent differences between pre-term and full term choline levels in another study [11165882].

In a small trial on 11 patients on long-term TPN, choline supplements over 24 weeks improved visual memory [11190987].

A good deal of research has gone into the hypothesis that mood disorders are due, in part, to an imbalance between monoaminergic and cholinergic neurotransmitters [C470, 10837844]. Brain scanning studies in both adults and teenagers have shown that choline status in several specific brain sites (such as the anterior cingulate gyrus and basal ganglia) was associated with bipolar disorder, their depression scores and their response to antidepressants [11249799, 11094138, 9099409]. In adults, there was an association between higher levels of plasma choline and lesser levels of anxiety but not with symptoms of depression in a study of 5,918 normal individuals from Norway [19656836].

No effect on memory was seen in two small, short-term controlled trials in which from choline was given to normal young adults and elderly subjects [7350901, 7266731]. A modest effect has been seen in some open trials, including medium term [3313362, 472728]. In a small open trial, choline supplements improved clinical status of bipolar patients, with concomittant increase in concentration of choline and its metabolites in the basal ganglia [8874839]. Lecithin produced some improvement in symptoms in a small placebo-controlled trial of 6 manic depressives [7051871].

In Alzheimer’s disease there is good evidence of degeneration in cholinergic neurons in the basal forebrain [1716012], and anticholinesterase inhibitors have been extensively trialled. However, such pharmacological approaches are outside the scope of this review. Within its scope is the small trial of lecithin in this disease which did, however, fail to produce any significant benefit on mood or cognitive state [2655861]. A number of trials have involved the choline precursor citicoline, and were conducted in elderly patients with varying levels of memory impairment, and have mostly had positive results, although not of large degree [18377103, 10669911]. A meta-analysis published in 2002 included 14 trials and concluded that there was “some evidence that CDP-choline has a positive effect on memory and behaviour in at least the short to medium term. The

evidence of benefit from global impression was stronger, but is still limited by the duration of the studies" [15846601]. It also shows some promise as a neuroprotectant agent in recovert from brain trauma [17171187]. There have been a few small trials of other choline precursors [17331541] and on its metabolite betain [11522934]. A recent randomised, controlled trial of a multinutrient supplement containing choline (along with essential fatty acids and the RNA nucleotide uridine) improved delayed verbal recall task score in 225 Alzheimer's patients after 12 weeks [20129316].

Niacin

Niacin (a term which encompasses nicotinic acid and nicotinamide) is the precursor to the pyridine nucleotide nicotinamide adenine dinucleotide (NAD), which in various forms is involved in energy metabolism, and serves as precursor to cyclic ADP-ribose, an intracellular Ca signalling molecule that plays an important role in synaptic plasticity in the hippocampus [19079853]. Niacin intake should be considered in conjunction with that of tryptophan, since the latter can be converted into the former. The classical niacin deficiency disease is pellegra, which features a trio of dermatitis, diarrhoea and dementia. For this reason the question arises as to whether niacin has some role in relation to cognitive function during aging and dementia. Although there have been some associations reported in observational studies between dietary niacin status and the risk of Alzheimer's disease or cognitive deterioration, as always these are subject to many confounding influences [15258207, 8988908]. A trial of nicotinic acid on 96 healthy subjects of various age groups from young adults to elderly over 8 weeks resulted in some significant improvements in memory test scores [3936095] but we lack confirming trials. Although it was a favourite vitamin in the orthomolecular movement for psychiatric treatment, there is little controlled trial evidence to support this use [1828703].

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Chapter xx: Homocysteine and vitamins B_{12}, folate and B_6

Executive summary

Vitamin, B_{12}, folate and B_6 are all crucial factors in one-carbon metabolism, within the interlocking folate and methionine cycles, the latter involving the generation and conversion of homocysteine (Hcy). Hence these vitamins are sometimes referred to as `Hcy-vitamins'. They are crucial for methylation and other reactions involved in synthesis and renewal of DNA, neurotransmitters and hormones. Vitamin B_{12} has a direct role in myelination.

Deficiency of these vitamins results in well established damage to the development of the central nervous system, for example neural tube defect in the case of folate deficiency during pregnancy, and sub-acute combined degeneration of the cord in B_{12} deficient infants. By impairing conversion of homocysteine (Hcy) to methionine in the methionine cycle or to serine, deficiency of these vitamins results in elevation of Hcy levels, which in turn has its own multiple potential pathological effects on the CNS, including directly on neuronal tissue and indirectly through circulatory insufficiency from damage to the cerebrovascular system.

Over 250 papers have documented the observational connection between Hcy, the Hcy-vitamins and cognitive states, in healthy subjects, those with psychiatric illness (particularly depression), older subjects experiencing the normal cognitive decline of aging, and those with pathological cognitive impairment, whether mild, moderate or severe (and including Alzheimer's disease). The large majority were in older subjects. The overall trend of the results of these studies was to find significant associations, particularly for Hcy, to a lesser extent folate and B_{12}. However, because of the often small subject numbers, variations in the measures and standards used for assessing both vitamin status and cognitive function and other methodological issues, the five systematic reviews and/or meta-analyses cited in this chapter did not reach a consensus conclusion on how strongly the evidence supports these links.

There have been around 100 papers published describing clinical trials in which the Hcy-vitamins have been used, in a wide variety of subjects which have included those with in all the above clinical categories, as well as with unknown, normal or abnormal baseline vitamin and Hcy status, and in which the reported outcome included cognitive measures. Again the majority have been in the elderly and cognitively impaired. The methodological issues mentioned in the preceding paragraph apply equally well if not more so to the collective body of clinical trials, and in addition many of them were not properly randomised and controlled. It is therefore not surprising that not a single one of the ten systematic reviews/meta-analyses cited in this chapter was able to conclude that the evidence currently available confirms a role for such supplementation in relation to cognition, dementia or depression.

Nevertheless, the overall scope of that evidence suggests that this lack of conclusiveness is more likely to be due to lack of methodological strength in the published literature than to there actually being no clinically applicable causal connection between Hcy-vitamin status and cognition. We must bear in mind the prevalence of marginal status of some of these nutrients, particularly in the elderly (along with some specialised high risk groups such as vegans). In the Australian context this is most likely to apply to vitamin B_{12} and to folate in those otherwise higher nutritional risk individuals who do not consume folate-fortified foods. And it is possible that folate fortification has increased the population risk that patients with marginal B_{12} deficiency will suffer neuropathology.

For all these reasons, an awareness of the status of these nutrients is well justified in ensuring both good public health and providing individual clinical care in relation to cognition.

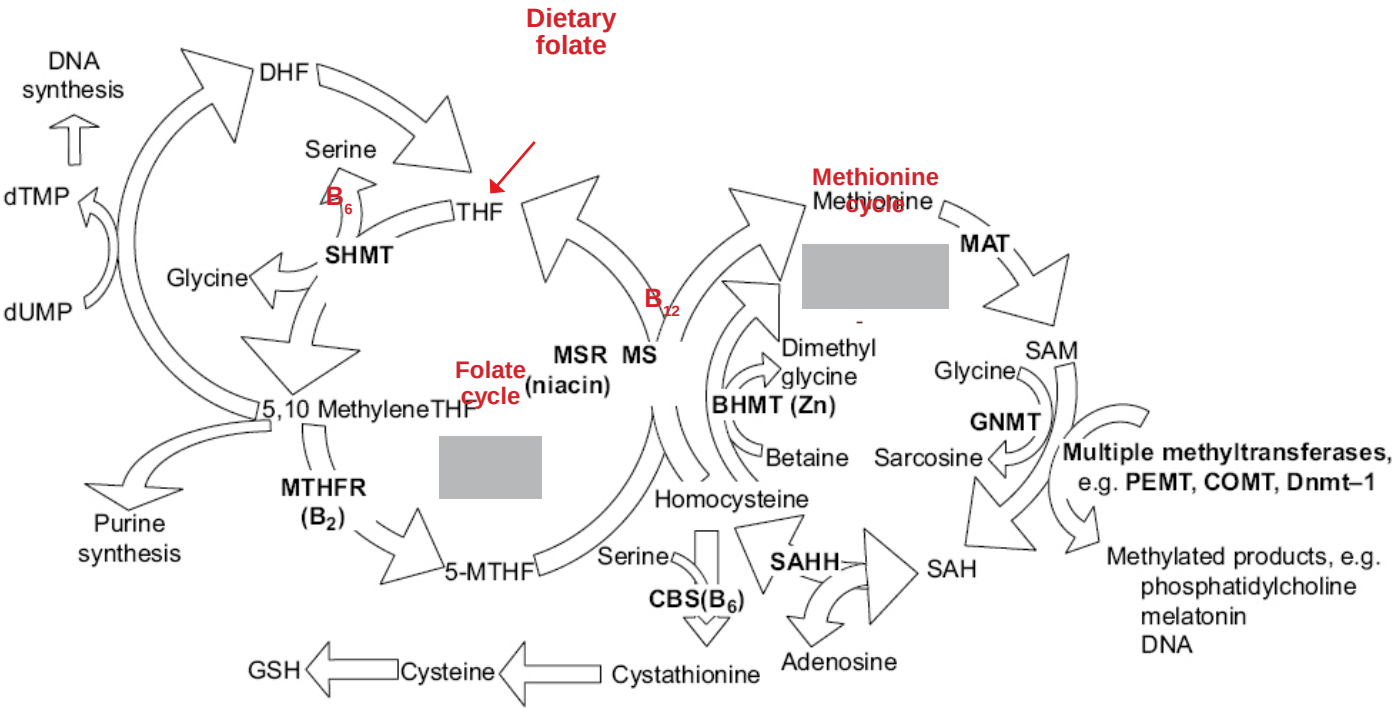
Physiology and pathophysiology

The relevance of folate, vitamin B_{12} and to a lesser extent vitamin B to the function of the nervous system

has been known for the better part of a century [13134642]. The core relationships between these and other so-called `homocysteine' (Hcy) nutrients in one-carbon metabolism is shown in Figure H1 below.

The figure highlights how the folate and methionine cycles are linked, with the former contributing methyl groups to form methyl-cobalamin, which is a crucial substrate for the step within the methionine cycle in which Hcy is converted to methionine. It shows how the folate cycle is itself driven by the B_6-dependent conversion of tetrahydro- to 5,10-methylenetetrahydrofolate (MTHF). The methionine cycle produces S-adenosylmethionine (SAM, sometimes abbreviated as SAMe). This is an extremely important compound, as the driver of a whole range of methylation reactions, including those involved in synthesis of neurotransmitters and hormones (such as melatonin) and of DNA. In the other linked metabolic cycle, MTHF is used in the synthesis of purines and DNA. In addition, Hcy is converted, courtesy of the contribution of the amino acid serine, to cysteine and glutathione, which process also requires vitamin B_6 [19079880, 10341670].

Figure H1: One-carbon metabolism (adapted from [19079880, 18950248]).
MS = methionine synthetase; SAH = S-adenosylhomocysteine, GSH = glutathione



The role of one-carbon metabolism in brain function is crucial and widespread. For example, methylation reactions include synthesis of essential phospholipid (phosphatidylcholine) and various monoamine neurotransmitters (such as serotonin, melatonin, epinephrine and dopamine) [18950248, 15472418]. Animal studies have shown that changes in one-carbon metabolism affect the proteins involved in neuronal plasticity and mitochondrial function [20930296].

For each of the Hcy vitamins, their indispensability for normal foetal and infant brain development and the devastating consequences of overt deficiency have been well established [10523053].

Folate
Looking at the individual nutrients, folate has a direct and specific role in purine and DNA synthesis (shown on the left had side of figure H1), as well as driving the SAM-based methylation shown on the right. Collectively this impact of folate on the genome may explain the well established link between folate deficiency and embryonic deficits of the nervous system, such as neural tube defect [20836042, 18709887, 8005024]. Folate deficiency has been reported as causing potentially reversible neurodevelopmental abnormalities manifesting in early childhood [15781839]. The exact mechanisms of folate's role in neurodevelopment are still being worked out, apart from a `generic' involvement in DNA synthesis, and may include, for example,

direct stimulation of embryonic neural stem cells [20838574]. Some degree of protection to borderline maternal folate insufficiency is afforded the foetus by the preferential concentration of folate at the expense of maternal stores. Nevertheless there is evidence of an effect of low maternal folate on infant birthweight, which in turn can affect psychomotor development [18709885].

This has been confirmed by important recent Australian research, in which infant birthweight was positively correlated with the mother's red cell folate at 20 weeks gestation (r=0.21, p=0.016), negatively with her Hcy level (p=0.044) (but not significantly with either B_{12} or B_6). Importantly, maternal Hcy was itself positively correlated with markers of genome damage in maternal blood at that time, which in turn is substantially (10+ x) more likely in those mothers whose pregnancies develop complications. Furthermore, both Hcy and uteroplacental insufficiency were linked with polymorphism of a gene encoding for the enzyme methionine synthase, which sits in a crucial position in the interlocking of the methionine and folate cycles in one-carbon metabolism (as per Fig.H1) [18771981].

At the other end of life, folate levels have been associated with the high level of DNA damage that is often seen in neurodegenerative disease [20219521]. Indeed, it seems entirely possible that the health of DNA methylation is one of the major factors in the maintenance (or deterioration) of learning and memory in the aging brain [17850924]. In animal models of Alzheimer's disease, both folic acid deficiency and excess Hcy impair DNA repair in hippocampal neurons specifically, and increase their sensitivity to amyloid toxicity [11880504].

Folate deficiency is quite common, with contributing factors including inadequate intake (e.g. the elderly), malabsorption (e.g. alcoholism, coeliac disease), drug interactions (e.g. anti-convulsants), elevated requirement (e.g. pregnancy, lactation) and excess excretion (e.g. alcoholism) [18709879]. On a population basis, folate levels have improved significantly in countries where folate fortification of food has been implemented, but obviously that does not prevent individuals being deficient (particularly those not consuming adequate amounts of such foods).

Vitamin B_{12}

The crucial function of vitamin B_{12} in myelination and hence its role in demyelination states such as sub-acute degeneration of the chord was established a long time ago [18447164], and the symptomatology of clinical B_{12} deficiency is quite consistent with this being a primary mechanism [1648656, 3374544]. But research continues on the fine details of where and how this happens (for example inflammatory response and imbalance between cytokine and growth factor imbalance in B_{12} deficiency), along with elucidation of other aspects of B_{12} neuropathy (e.g. disturbance to the blood-brain barrier) [19394404, 18454811, 18447164]. It remains unclear whether B_{12}-related pathology is involved in other demyelinating diseases such as multiple sclerosis [1430153]. It is well established that the neurological damage can occur without any signs of anaemia and that, whilst this may be reversible to varying degrees following B12 supplementation, it may not always be so [15805657, 12486445, 10713580].

Myelination of nerve cells is most active during the period from mid-gestation to the second year of life, but still continues to lesser extent through to puberty. Since B_{12} is preferentially concentrated into the foetal liver, the infant is protected to some degree from B_{12} deficiency until around 2 months post-partum. The reported case studies of neurological abnormality in children of exclusively breast fed infants of vegan mothers were in the second six months of life [18709887]. There was also an intriguing finding in one observational study that low levels of B_{12} in pregnant women were associated with higher risk of neural tube defect, independently of folate levels [8265769].

At the other end of life, what is notable about B_{12} is the specific tendency to impaired absorption with increasing age. Although geriatric malabsorption due to increasing loss of gut efficiency is seen with many nutrients, the problem is especially acute in the case of B_{12} due to its dependence on a highly specific absorption mechanism, and the vulnerability of that mechanism to the rapidly increasing incidence of gastric hypochlohydria and gastric atrophy, (a process that appears to be separate from lack of intrinsic factor, and thus quite distinct from what is seen in pernicious anaemia) [10681269].

Prior to old age, overt vitamin B_{12} deficiency is most usually due to inadequate consumption of animal foods that are its only sources, due to vegan or some poorly planned vegetarian diets. In the elderly malabsorption due to the falling efficiency of absorptive mechanism just referred to becomes important,

resulting in compromised B_{12} status. A wide range of prevalence estimates have been published for such marginal B_{12} deficiency, some as high as 50% of over sixty year olds. A more consensus figure for would be in the 15-20% range, particularly when using tests of B_{12} status with greater sensitivity (e.g. urinary excretion of the B_{12} metabolite methylmalonic acid) [19116323, 18709879, 9322547]. B_{12} malabsorption can also be caused by gastric and ileal illness (e.g. *Helicobacter pylori* infection, giardiasis, coeliac disease) and the effect of proton pump inhibitors [18709879].

Vitamin B_6

Pyridoxine and its related compounds have a direct involvement in amino acid metabolism and hence in synthesis of neurotransmitters, for example the cysteine pathway shown at the bottom of figure H1 [8414222, 10523053, 14584010]. This would explain the (admittedly limited) evidence that its relationship to cognitive disorders in the elderly is independent of Hcy levels [17260529]. Given the relatively wide range of vitamin B_6 food sources, clinical B_6 deficiency is usually the result of a more general malnutrition, some medical condition or drug interaction [17260529].

Homocysteine

Excessive Hcy in itself (along with elevated SAH) inhibits SAM methylation activity, and may be directly neurotoxic, as well as contributing to ischaemic brain damage through cerebrovascular atherosclerosis [20824535, 18709889]. In animal studies, for example, elevated Hcy leads to endothelial dysfunction of cerebral small vessels and impaired cerebral blood flow through increased carotid arterial resistance [14607791, 8725259]. (On the other hand, it is worth noting that, in a meta-analysis from 2002, elevated Hcy was found to be at most a modest independent predictor of IHD and stroke risk in healthy populations [12387654]). One paper referred to the combination of impaired methylation and cerebrovascular atherosclerosis contributing to mood disorders as “the homocysteine hypothesis of depression” [17541043]. There is some evidence that brain structures in the hippocampal area crucial for memory function are smaller in subjects with elevated total homocysteine concentrations [16102882, 12477704]. Other mechanisms by which one, several or all of these interacting factors may affect brain function and health include: neurotoxic activation of N-methyl-D-aspartate receptors, increased oxidative stress, interference in HDL generation through interaction with apoE, promotion of apoptosis and increased β-amyloid toxicity [20889503, 18709889, 18023533, 16155257, 15477631, 15472418, 11461960]. Abnormalities of methylation biochemistry have been postulated in various psychiatric disorders, such as depression, schizophrenia and autism [19079880].

Interactions

The interrelationships between these nutrients themselves and between them and Hcy are complex and not easily separated in clinical research, especially observational research and particularly when it comes to brain function. So, for example, one study showed that biomarkers for folate and B_{12} within CSF were intercorrelated, and correlated with CSF concentrations of Hcy and other measures of the methionine cycle [17200133]. This is relevant to a question that has received quite a lot of both clinical and public health attention - what is the relative contribution of the three Hcy nutrients to Hcy elevations and which would be the most effective nutrient supplementation regime to reduce elevated Hcy and the risks associated with it? A related issue is how this balance may have changed in countries where folate has been added as a fortificant to some staple foods.

One research team approaches this question within the broad US population by analysing data from blood samples collected as part of the national nutrition survey NHANES III. They found that the contribution to high total serum Hcy was much stronger for decreased serum folate status than for decreased serum B_{12}, and was greatest where both folate and B_{12} levels were low [10475885]. Another much more specialised population group that can inform this question are vegetarians, who typically may have very generous folate, adequate B_6 but marginal B_{12} intakes [3565307]. Studies have consistently shown that vegetarians, and especially vegans, have higher Hcy levels than omnivores [16697371 12816782, 12638029, 12460231, 12119198, 12011576, 11470726, 11375297, 11108902, 11053901, 10557004, 10479236, 10404767]. The question of relative impact of individual Hcy nutrients to what one could call `one-carbon metabolism pathology’ remains the subject of investigation with no single clear cut answer yet emerging.

Human observational studies

There is no shortage of observational data in this area - we considered over 250 papers. The large majority of the studies focused on the elderly, a lesser number on psychiatric states (particularly depression), and only a few looked at children and healthy adults.

Children

The potential impact of Hcy nutrient deficiency to neurodevelopment was suggested by a recent study from India which found that maternal folate concentrations during pregnancy were correlated with cognitive scores in the offspring of those pregnancies a decade later. This applied to measures of learning, long-term storage/retrieval, visuo-spatial ability, attention, and concentration, was independent of the parents' education, socioeconomic status, religion, and of the child's sex, age, current size, and current folate and B_{12} level. This was not seen in relation to either maternal vitamin B_{12} or Hcy [20335637]. A protective relationship was also reported between maternal folate supplement use during pregnancy and child behavioural problems at the age of 18 months [19772683]. On the other hand, no association was found between maternal folate status and offspring psychomotor or mental development at 5 years of age in an earlier American study [16140711]. Higher dietary intake of B_{12} (and of riboflavin, iron and zinc, but not of folate) was associated with better cognitive test scores in a 2 year longitudinal study of Kenyan schoolchildren [18826659]. A test measuring a "fluid intelligence" was correlated with B_{12} status in a case-control study of teenagers, but as the `cases' were former vegans, some of whom remained vegetarian, this may well have been confounded by other nutritional or lifestyle factors [10966896].

Another possible effect of folate is in its relationship to the damage caused to the CNS by excess levels of lead. In a Philippine study, higher levels of folate mitigated the negative association of lead levels [18206696]. An intriguing link in lead-exposed children from Mexico City was suggested by the finding that maternal MTHFR 677T allele was a predictor of poorer child neurodevelopment at 24 months independently of the child's genotype (this is a genetic polymorphism for the efficiency of the MTHFR enzyme shown in figure H1 as occupying a key role in the folate cycle). This suggested to the authors that the maternal folate metabolic environment in some way programmed the child's neurodevelopmental pathway [20504979].

The interface of polymorphism in the genetics of MTHFR and other enzymes, as it affects one-carbon metabolism and the impact on cognition, is a subject of interest at all ages, although still in early stages of investigation [20825473, 20670473, 19244370, 19019492, 18709878, 17684227, 12163693]. An example of the most recent research is the 2010 report of an association (at level $p<0.03$) between late-onset Alzheimer's disease and a polymorphism in the gene encoding for the enzyme methylenetetrahydrofolate dehydrogenase, which is directly involved in the methionine cycle [20885792]. A meta-analysis published in 2010 of 19 observational studies on the link between Alzheimer's disease and the MTHFR C677T polymorphism found that there was such an association, but that, after controlling for the much more substantially established association with apoE genotype, this correlation was not present in Caucasians, but was for East Asians [20600372].

Adults

A report from the Framingham offspring cohort found that in the sub-set of subjects aged 40-49 years (and the sub-set aged 50-59 years) there was no correlation between serum Hcy levels and cognitive performance [16107567]. An Australian cross-sectional study found positive association between memory function on the one hand and dietary intake of vitamins B_{12} and B_6 in men, and moderate dietary intake of folate and B_6 in women on the other [15316586]. In another study of healthy adults, lower serum B was

associated with decreased performance in the Stroop Color-Word Test (a test of attentional vitality and flexibility) [C269]. A longitudinal study over six years of a cohort ranging from 30 to 80 years of age found negative correlation between Hcy and cognitive test scores regardless of initial age, but the total sample was only 144 people [12766792]. In a curious recent German experiment, 100 healthy medical students had cognition tested at breakfast and lunch on the same day, at which times the Hcy levels were varied by means of selective fasting. Such extremely short term elevations in Hcy did not have any short-term impact on the subjects' cognitive test scores [20305995].

Another set of data relates to subjects with psychological or neurological illness. A significant number of studies have reported some correlation between depression of various types, Hcy and the Hcy nutrients. These associations have been seen in various cultures, age groups, both genders and in relation to the risk of the disease, its severity and the response to antidepressant treatment (including timing, proportion of responders and relapse rate) [2763862, 2720001, 2145341, 20087384, 2005338, 20032481, 19484842, 18503720, 18378986, 18061404, 16297603, 15877935, 15479988, 15323595, 15323594, 14641930, 12601225, 10784463, 9054796]. There is some, but not nearly as much, evidence of associations between these factors and bipolar disorder [18399726, 17490752, 17391351, 9479613]. There is also a small amount of data showing low SAM levels in depression [2292704, 12420702]. In patients with Parkinson's disease, those with lower folate levels had more depression, and those with lower B_{12} levels worse cognitive test scores [18055246].

Elderly

Similar relationships between these vitamins and depression have been reported in the elderly [2294976, 20519557, 17320847 , 15447915,], though not in all studies [11813081]. However, by far the majority of observational studies in this age group relate to overall cognitive performance. These can be divided into those that deal with Alzheimer's disease and related dementing states, and those that deal with the general cognitive health of the elderly, including what one might regard as being within a `normal' range of cognitive decline with increasing age. This leaves moot the thorny issue of how clearly dementia can always be distinguished from `normal' cognitive decline, both from a clinical and mechanistic perspective. In this review, of course, we are only concerned with pathological states in so far as they throw light on normal cognitive function.

Certainly there are plenty of studies that show associations between Alzheimer's disease and one or more of higher Hcy or lower status of the three Hcy vitamins. This includes both longitudinal data and some evidence of dose-response impact with disease severity (e.g. [15065230 ,11342684, 10822240 , 10731508, 9060973, 1456073]). In two very recent papers, Hcy levels showed correlation with cognitive decline in this disease over both six months [20824536], and more strongly over a decade time span, even when these those levels lay within the `normal' range [19484711]. However, by no means all studies have reached the same conclusion. So, for example, recent studies from the UK and from Holland did not find such an association [20836918, 10430233]. As with depression, the possibility of a disturbance of one-cycle metabolism is supported by the finding in several studies of low levels of SAM in the CNS of Alzheimer's patients [2292704, 8752143]. Prospectively, a new 2010 study used a more sophisticated measure of B_{12} status (holo-transcobalamin) as well as Hcy to estimate the risk of developing Alzheimer's over 7 years in a group of older subjects (65-79 years) initially free of dementia. The odds ratio for incident Alzheimer's in that period based on initial biochemical values was 1.16 (95% CI: 1.04–1.31) per increase of 1 mol/L of Hcy and 0.98 (0.97–1.0) for each increase of 1 pmol/L holoTC [20956786].

There are also a good number of studies showing a link in the second category referred to above, i.e. with `normal' aging in regard to cognitive function and decline (e.g. [19171834, 18835069, 18451312, 17823439 , 17537289, 17158436, 15207433 , 15694902]). It is notable that these relationships appeared to operate across a wide range of low to normal vitamin levels, not just overt deficiency [19116332, 17991650 , 17823439]. One interesting study (though reported with scant detail) in which IQ scores were available for each subject at both age 11 and age 79 years reported that vitamin B_{12} at 79 years correlated with cognitive decline in IQ over this substantial 68 year period ($p=0.011$) [15654057]. A small prospective British study of 107 initially cognitively intact, community dwelling elderly (61-87 years of age) found that found that the rate of brain volume loss over time was associated with both serum B_{12} and holotranscobalamin (a B_{12} metabolite which some believe may be a more sensitive marker of functional B12 status) [18779510].

Although individual studies have found different aspects of cognition linked with levels of one nutrient or Hcy compared with the others (e.g. [17158436]), there is no consistent evidence for such cognitive specificity, and one must bear in mind the wide range of cognitive tests employed across the various studies. (As a side note, general rather than regional blood flow increases were seen in mildly demented patients whose cognitive state improved after B_{12} therapy in an uncontrolled Swedish trial [10965378]). Nor is there consistent

evidence for the notion that the relationship between low B_{12} and worse cognition is modified by high folate status or vice versa , although some have suggested that, in this era of folate fortification, the role of B_{12} deficiency in relation to cognition has become more significant [19141696 , 18341758 ,17209196]. (This is on a public health level, and is separate to the concern for an individual patient that folate supplementation can contribute to the neuropathology of B_{12} deficiency, either by countering the macrocytic anaemia that might

otherwise be the conventional first sign of deficiency, or by driving the metabolic cycles shown in Fig.H1 beyond its `B_{12} capacity', in the face of marginal B_{12} status [18709891, 17972439]. Another important point is that these associations also apply to what one could consider the border between the two categories (dementia and normal aging), i.e. what is often called mild cognitive impairment and which is usually considered to be an early stage of what may later progress to dementia (e.g. [19088473, 17709448, 17284751, 15213037, 16197304]). On an anatomical level, this association appears to be reflected in the link seen in several studies between Hcy, B_{12} and folate levels and abnormalities of white matter, such as atrophy or hyperintensities on brain scan [20374668, 18977824, 18350363, 17823439, 15545331]. See Figure H2. Whether this is cause, effect or co-morbidity is not clear, and at least one study in healthy elderly subjects did not find any such link [12557288].

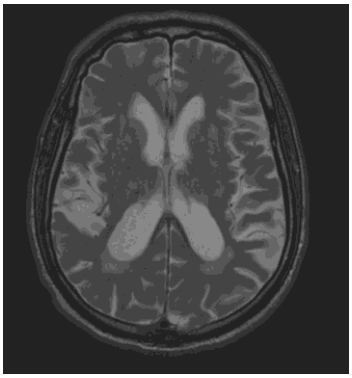


Figure H2: White matter hyperintensities in non-specific cognitive decline

Systematic reviews

There have been five reasonably systematic collations of this observational evidence. One which was published in 2007 examined 24 studies, both cross-sectional and longitudinal, which looked at levels of one of more of the three Hcy vitamins in relation to cognition in the elderly. Ten studies involving 2,910 subjects were on cognitive decline, whilst ten studies on 3,966 subjects focused on Alzheimer's disease (there were no overlaps). Methodological quality in most was considered only "fair" and heterogeneity was high - 30 cognitive tests had been used across the various studies. Their conclusion was that: "there is no significant association between blood concentrations or the dietary intake of vitamin B-6 and B-12 and cognitive-test performance or Alzheimer's disease", although they were a little more positive for folate and Hcy [17585032].

Another review from 2008 identified 29 studies on vitamin B_{12} and cognition, most of which had methodological limitations, and found very little consistent evidence of a correlation. For folate the evidence was somewhat stronger [18709888].

After reviewing both observational and randomised, controlled trial studies, a meta-analysis published in 2010 could not find sufficient evidence to draw clear conclusions on the association of B vitamins (or fatty acids) and cognitive decline or dementia [20847412].

The authors of a meta-analysis published in 2009 identified 9 case-control studies on Alzheimer's (including the pre-clinical phase) which they assessed as being of good quality (n=1,334). They calculated the standardised mean difference in Hcy levels between cases and controls to be 1.04 (95% CI: 0.44-1.63), whilst that for lower folate was 0.65 (95% CI: 0.34-0.95, n= 699) and for vitamin B_{12} 1.50 (95% CI: -0.05-1.06, n=699) .

A slightly earlier review from 2008 also reached a positive conclusion. The authors identified 77 cross-sectional studies on 34,238 subjects and 33 prospective studies on more than 12,000 subjects that reported associations between cognitive deficit or dementia and Hcy and/or B vitamins. Only 7 cross-sectional studies on 3,645 subjects did not find this [18709889].

The lead author of that review, in another paper [19116332], put forward some reasons why different reviews have not reached a firm consensus conclusion. Because cognitive decline on the one hand, and impaired diet and absorption (including specifically for B_{12}) on the other are both very common the elderly, the

potential for confounding or reverse causality is even greater than usual. Clearly, people with impaired cognition are more likely to eat poorly, and this will have obvious impact in populations where dietary deficiency is already relatively common in the non-demented population (e.g. folate in countries without folate fortification of staple foods) 2750771, 18843658. Some have argued that Hcy may be a confounder because it is a general marker for a healthy diet 17556678. Other challenges include: wide variation in the cognitive measures used, insensitivity of the nutrient tests most commonly reported (particularly in relation to their status within the CNS, for which we have scant data in any case 18709889), uncertainty about whether there are threshold levels for Hcy and these vitamins for cognitive impact and if so what these might be, not accounting for the baseline status of the nutrients in the population studied across time (e.g. as folate fortification has been introduced in some countries).

Clinical trials

A significant number of trials have been conducted using the Hcy nutrients as supplements and including cognition as an outcome - around 100 papers have been considered in this review. As with observational studies, these can be grouped by age group and by whether the patients had dementia. Most were conducted in the elderly.

Children

Direct trials on psychocognitive outcomes have involved multinutrient supplements. An iron-folic acid combination given at least twice per week to primary school girls in India over a year resulted in significant improvement in cognitive tests, but this may have been more due to the iron, as the result was more pronounced in those who had initial anaemia and who responded with raised haemoglobin level 19242031. This finding was similar to the outcome of another Indian trial reported nearly thirty years earlier 7115656. A wide-spectrum B group fortified food supplement improved cognitive test results in Chinese primary school children 16883966, and a multinutrient supplement had similar impact on motor scores of high risk Bangladeshi infants 18326610. A number of trials relate to autism and similar neurodevelopmental states, for which there is some evidence of abnormalities of monoamine neurotransmitter levels, particularly dopamine 8567594. On that basis, the trials (a few of which were on adults) have used a combination of vitamin B_6 and magnesium. A review from 1995 identified 12 such trials (but from only four different research groups), the majority of which reported positive findings, but with small samples and short duration 8567594. Since then three further trials have been reported, a 10 week double-blind trial on 10 autistic children which did not show any benefit in symptomatology 9261669, a four week trial on 8 children and a six month trial on 33 autistic and 36 control children both of which did show benefit 11995900,16846101. Clearly this is an unresolved issue, and in any case the relevance of this to normal cognition is uncertain.

Adults

Supplements of each of the three Hcy vitamins taken individually for 35 days had significant effect in improving some tests of memory performance in both young, middle-aged and older healthy women in an Australian trial 12042457. A combination of all three vitamins given together over an average of 5.4 years to health professional women over the age of 39 years and at high risk of cardiovascular disease did not result in any significant overall impact on telephone conducted cognitive tests, but did preserve cognitive function in those women with low baseline B vitamin intake 19064521. In a recent English trial, a broad spectrum B complex with vitamin C given to healthy men aged 30 to 50 years for 33 days resulted in improved cognitive performance under stressful testing 20454891. There was no cognitive impact of B_{12} injections given weekly to healthy adults over a 14 week period in another small trial 5414901.

Looking at psychiatric conditions, the effect of an antidepressant was augmented by concomitant folate supplementation in an English trial of 127 depressed patients 10967371, as was the effect of lithium in another trial 2939126. It is possible that folate supplements have this effect in part because of increased accumulation of serotonin - some evidence for this has been seen in lymphocytes 18716414. A much larger trial of folate in depression in a community setting is currently in the planning stage 18005429. A rather vaguely defined clinical sample of 50 elderly folate deficient patients with “behaviour disorders” (some were depressed, some demented) were given parenteral folate and tested on behavioural and mood scales. They showed significant improvement C457. There was no cognitive or antidepressant effect of giving B_{12} supplements to patients with biochemical evidence (increased plasma methylmalonic acid) of B_{12} deficiency in a Danish trial 15337331. Another mood disorder in which a potential role has been suggested for vitamin B_6 because of its specific involvement in serotonin synthesis is premenstrual syndrome 11207460, 10341670, and some trials testing this hypothesis have been conducted 10341670. Several trials (some open, some controlled) have used

SAM directly in depression, with encouraging results, for example the finding of an efficacy equal to that of imipramine but with less side-effects [3046382, 2183633, 15538952, 1289923, 12418499, 12420702,11104210], as was suggested by a systematic review conducted back in 1994 [7941964]. Although SAM has been proposed as a treatment for dementia, there have as yet been no controlled trials [2292704, 18334758].

Elderly

In non-demented subjects, vitamin B_6 given to healthy 70 year olds modestly improved information storage [1365868]. In a new Australian trial, B_6 in combination with vitamin B_{12} and folate administered to 70+ year old men with hypertension produced no cognitive benefit [20861451], although the level of β amyloid was reduced [17113685]. In subjects with biochemical B_{12} deficiency, giving vitamin B on its own did not improve

Mini-Mental State Examination scores in an Australian trial lasting one month[12] [12028259], or cognitive outcomes in a Dutch trial lasting one year (including when folate was added) [16895884], nor measures of cognition or depression in either a Scandinavian or an English study, both of which lasted three months [16709605, C461].

Amongst Dutch elderly, supplements of B_{12} and folate given for 24 weeks resulted in non-significant improvement in cognitive performance only in those in whom betaine levels rose (betaine is one of the one-carbon metabolites), but there was no relationship between cognitive change and the fall in Hcy that occurred [17537289]. There was no cognitive benefit from giving folate to healthy elderly in a British trial, but this is hardly surprising considering that there were only 24 subjects, their baseline folate was normal, and the treatment lasted only 4 weeks [16359741]! Nor was there cognitive benefit for elderly patients given the Hcy vitamins for four months [15883442], two years (a study from New Zealand) [16807413], or the same plus riboflavin for one year [16332666].

The FACIT trial was an important Dutch contribution to our knowledge in this area because, on contrast to the methodological weakness of some of those trials, it had careful design, good study numbers and a reasonable treatment duration. Over 800 subjects aged 50-70 years, who had elevated Hcy but normal B_{12} levels, were given folate or placebo for 3 years. Compared with placebo, the folate group had significant significantly greater falls in Hcy and better outcomes in terms of changes in memory, information processing and sensoromotor speed [17240287].

In subjects with mild cognitive impairment, a combination of all three Hcy vitamins slowed the rate of brain atrophy over 2 years of treatment [20838622], but did not improve cognition over one year in another trial [18308888], although it did improve blood-brain barrier function in a Swedish study where there was initially elevated Hcy [12826740]. Vitamin B_{12} therapy in deficient patients with mild cognitive impairment improved cognition, but was of no value when the patients were already demented [10713580]. In 30 patients with “abnormal cognitive decline” and low folate levels, two months of folate supplementation resulted in a significant improvement on both memory and attention efficiency, compared with placebo [18653121]. Folate and B_{12} did not change cognition when given to patients with dementia or mild cognitive impairment [12823643].

In demented patients, results have been mixed. The trial mentioned immediately above found no benefit from B_{12} in deficient patients, nor did a more recent one [18925978], although a third did [12486445] and a fourth reported less delerium but no cognitive change [17561285]. A fifth trial using B_{12} and folate together was also positive [11424170]. Eighteen months of high dose Hcy vitamin supplementation did not slow the rate of cognitive decline in a double-blind trial on 340 Alzheimer’s patients [18854539], nor did four months of B_{12} affect cognitive scores when given to 50 B_{12} deficient Chinese Alzheimer’s patients [9777425]. An uncontrolled Dutch trial of B_{12} given to both those with and those without deficiency did not result in improvement in dementia [8836942], whereas in another uncontrolled trial improvement from B_{12} supplementation in deficient, cognitively impaired patients was only seen in those whose symptoms had lasted less than 12 months [1740602]. Adding folate to cholinesterase inhibitor therapy improved some measures of Alzheimer’s patients’ behaviour in a recent Scottish trial [17600848]. A non-significant trend to cognitive improvement after folate supplementation of demented patients with low to normal baseline folate cannot be interpreted due to the tiny size (n=7) of the trial [12967058]. Nor can one draw any conclusions regarding the role of the Hcy vitamins where these were simply components of a much broader multinutrient supplementation in two other trials (one had positive cognitive outcome and the other not) [19056706, 18042476].

Geriatric depression has been treated with folate, with reduced symptom severity in two double-blind and one open label trial [8257478,1974941, 8348200]. Borderline improvement was obtained in a small, short-term study using B_6 together with thiamine and riboflavin [1578091]. No change was the result of 2 years of Hcy vitamin therapy in an Australian placebo-controlled trial [18557664].

Meta-analysis and systematic review

It is easy to gain the impression from looking at all the above trials that, whilst the predominance of evidence is positive, the story is very mixed and fraught with methodological weakness, particularly substantial heterogeneity between trials, small sample sizes and in many cases short durations in relation to the slow progress of cognitive decline. That such an impression is not misleading is confirmed by the various meta-analyses that have been conducted in this area:

1. Cognition (including cognitive decline and dementia)

Seven systematic reviews have been published in relation to cognition. A Cochrane meta-analysis (updated in 2008) initially considered 98 papers involving folate with or without B , but only eight trials

met its methodological criteria (one half were in demented and one half in non-demented subjects), on a total of 1,317 subjects (nearly two thirds of them from one study). The authors concluded that there was "no consistent evidence either way that folic acid, with or without vitamin B_{12}, has a beneficial effect on cognitive function of unselected healthy or cognitively impaired older people" 18843658.

The same lead author published another Cochrane review focused on B_{12} and cognition, updated in 2009, in which only three trials involving 183 subjects were found worthy of inclusion (8 further trials were excluded). Unsurprisingly with such small numbers, the conclusion was that there was no evidence of an effect 12918012.

A systematic review without meta-analysis published in 2010 concluded that some B_{12} deficient patients with mild dementia might show benefit from supplementation, but there was scarce evidence for benefit in severe dementia 20505848.

A meta-analysis on the three Hcy vitamins (separately or together) for cognitive function published in 2007 found 10 trials with 14 treatment arms on 707 subjects which met their criteria. These used about 50 different cognitive tests. The authors concluded that the data did not yet provide evidence of an effect 17210874.

A meta-analysis published in 2010 identified randomised, controlled trials on B vitamins. They also looked at observational studies (as well as studies on fatty acids) and their overall conclusion was that: "the available evidence is insufficient to draw definitive conclusions on the association of B vitamins... with cognitive decline or dementia" 20847412.

Another meta-analysis from 2010 included 9 randomised trials (on 2,835 participants, with median duration 6 months) of folic acid, and found no effect on cognitive function within a follow-up period of 3 years after treatment had commenced 20569758.

The seventh meta-analysis was from 2003. It focused on vitamin B_6 and cognition. It included only two trials, both on healthy subjects, including a grand total of 109 subjects, including placebo controls over 5 and 12 weeks respectively! As one might expect, since neither trial had positive outcome on cognition or mood, the authors were unable to conclude from this meagre data set that there was any benefit in this regard 14584010.

2. Neuropsychiatric disorders

A Cochrane meta-analysis published in 2004 examined three randomised trials of folate or placebo in 247 depressed subjects. Their conclusion: "The limited available evidence suggests folate may have a potential role as a supplement to other treatment for depression. It is currently unclear if this is the case both for people with normal folate levels, and for those with folate deficiency" 12804463.

Another Cochrane meta-analysis looked at the question of vitamin B_6 treatment (with magnesium) in autism. As it could only muster 3 small studies with methodological limitations, no recommendation could be made 16235322. A review in 1990 of trials of vitamin B_6 for premenstrual syndrome found 12 worthy

of consideration, but concluded that the evidence supporting a benefit was weak [2242373]. Nearly a decade later in 1999, 9 trials for this application were included in another systematic review, and in relation to the specific symptom of depression the odds ratio for improvement was 1.69 (95% CI: 1.39-2.06, based on 4 trials with n=541) [10334745].

Conclusion

Whilst there is good basic science showing the importance of the Hcy vitamins to neural development and cognitive function, clear evidence of neuropathology in overt deficiency states, any number of interesting observational studies linking their status to cognitive health and decline, and a reasonable number of positive clinical trials, the conclusions of these systematic reviews do not give grounds for any firm recommendations that can be applied in clinical practice.

One could readily argue that this is because of the lack of numbers, duration and consistency of approach across those trials, rather than problems with the hypothesis itself [15883414]. One could suggest that the formulation of the supplements used was ineffective, for example that 5-methyltetrahydrofolate rather than folic acid is the better formulation, or that higher doses may be needed to normalise cognitive deficits than are required to reduce Hcy [19909688, C466, 15883414]. Or that the focus of the majority of studies has been on supplementation in people whose cognitive deterioration was too advanced to respond, particularly in the time frames allowed in those trials. Others have pointed out the difficulties created when trying to view the one-carbon cycle in isolation from the status of the metabolic pathways that interconnect with it, for example essential fatty acid synthesis [18827306].

What is clear is that further randomised trial data will be needed to resolve this question. One hopes that these will justify the optimism of one author who wrote: “consistent data are expected from upcoming clinical intervention trials” [18089953]. Some of this data may be available from a number of recent or ongoing trials in which interventions designed to reduce elevated Hcy levels had primary end-points other than cognition (e.g. cerebrovascular disease) but which measured cognition along the way. A review in 2008 identified a dozen such trials involving around 52,000 subjects [18234134]. On the other hand, it must be said that the results for the primary end points of such of these trials as have been completed to date have mostly not been overly encouraging [C468].

In the meanwhile, the evidence that we already have suggests that, at the very least, Hcy is a strong marker for cognitive decline in the elderly. And that, on balance, the Hcy vitamins most likely have a causative role in cognitive outcomes, even though the clinical trials reviewed above have clearly failed to produce consistent evidence of benefit from supplementing with them. What has to be borne in mind, as discussed above, is the prevalence of deficiency in the population. This is most relevant in the elderly, in relation to vitamin B_{12} and in those whose dietary intake does not benefit from the folate-fortification of food staples. In adults and children it is more specific at-risk groups for whom this is most likely to be relevant, for example vegans and those with gastrointestinal disease. In pregnancy the status of vitamin B_{12} and folate in particular are of direct and immediate relevance to cognitive and neurodevelopmental outcomes.

For all these reasons, an awareness of the status of these nutrients is well justified in ensuring both good public health and providing individual clinical care in relation to cognition.

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Chapter xx: ZINC

Executive summary

The effect of zinc on cognition is wide-ranging and has been established by a considerable number of animal, human observational and clinical intervention trials.

Most CNS zinc is protein bound, and has central role in DNA transcription and protein synthesis. Unbound zinc is concentrated within `gluzinergic' neurones, especially in the corticolimbic areas of the brain, and is involved in neurotransmission at the neuronal synapse. Both bound and unbound zinc have an important function in brain plasticity, especially memory. Zinc concentration is especially rich in the hippocampus. Zinc homoeostasis is crucial to its function, not least because zinc in excess is neurotoxic, which seems to be involved in the brain's response to trauma, ischaemia and aging.

Zinc deficiency states have a range of CNS symptoms, including deficits in memory, special senses and mood. In animal studies, zinc deficiency affects cognitive development by decreasing activity, increasing emotional behaviour and impairing memory and the capacity to learn. There are particular periods of vulnerability at times of high growth, such as during pregnancy and childhood.

Several dozen human clinical trials of zinc supplementation have reported cognitive outcomes. Though the trend is clearly towards positive results, the variations in subjects studied and methodology do not allow firm conclusions to be reached on the basis of that collated trial data.

Nevertheless, looking at the totality of animal, human observational, depletion/repletion and randomised clinical trials, we can reasonably say that:

1. Zinc is crucial to cognition, particularly corticolimbic functions such as memory and mood.

2. Zinc supplementation sometimes benefits cognitive function, and this is more likely in those with prior zinc deficiency.

However:

3. It is not always possible to reverse damage done by zinc deficiency, especially if it occurs during vulnerable periods of brain and body growth.

4. Because of the potential for toxicity and interaction between minerals, naturally balanced sources of zinc, such as found in animal foods, are likely to be the safest means of zinc enrichment.

Physiology

Zinc is the second most abundant trace element in the human body, with total content averaging around 2 gm, which is about half that of iron and 10-fold that of copper 7082716. Zinc is involved with a very wide range of proteins, especially enzymes. Over 300 proteins require zinc to function, which is more than for any other essential trace metal 16308485, 11831464, 19747942. It has been estimated that around 10% of the human genome encodes for proteins containing zinc-binding sites 19026685.

Zinc plays a role in protein structure, as an enzyme catalyst and in regulation of DNA transcription and replication 19623531, 19026685. As well as a function in transcription and regulation, zinc has a stimulating effect on growth factors such as insulin-like growth factor and thymulin and possibly on thyroid hormones, and in energy utilisation C227, 11509097. Combining all these roles, zinc can be considered as a `growth nutrient', and this is true whether one is looking at the level of an individual cell, or of a whole child 16491666, 15235141, 12044825, C123, C227!

Brain function

The central nervous system (CNS) holds about 10% of the body's zinc content, also more than any other metal except iron 9391032. It is involved in key events across the whole life cycle of the neurone, including proliferation, migration, differentiation, and survival C123. Indeed, the diversity of actions that zinc has within the body generally is matched by a similar diversity of roles it is believed to have within the CNS - see Table Z1 below.

Table Z1: Areas of influence of zinc in the CNS 19623531

Apoptosis	Neurogenesis
Audition	Neuromodulation
Free radical management	Neuronal migration
Hormone activity	Nociception
Immune efficiency	Olfaction
Intracellular signalling	Protein structural conformation
Learning and memory	Regulation of enzyme activity
Motor coordination	Synaptic plasticity
Motor coordination	Synaptogenesis
	Vision

Of these many functions, two are particularly prominent for cognition and will be discussed in detail in this review. At the individual neuronal level, zinc has a prominent role in neurotransmission. At a higher level of brain organisation, zinc is involved in changes in structure and function that allow for brain plasticity and the formation of memory. In reality, it seems likely that the two functions are closely interrelated. As we will see, zinc's role in neurotransmission includes action on post-synaptic receptors and it has the capacity to change them in ways that facilitate the short-term and long-term changes associated with plasticity. Other avenues for influencing plasticity include protein regulating functions by the zinc that is bound up within zinc metalloproteins (in both neurons and glial cells), as well as its role in apoptosis and hence with the turnover of brain cells 11113504, 15452827.

The large majority of zinc in the brain (around 90%) is bound up in zinc protein complexes, such as the matrix metalloproteinases 17635123. The remaining 10% is concentrated within a specific class of neurones.

The zinc bound in protein complexes serves the structural and gene regulatory roles mentioned above. The most important are known as *zinc finger proteins*. These have many functions, but an extremely important one is in the transcription of DNA, and in fact zinc finger proteins make up a significant proportion of all the body's DNA-binding proteins 16308485, 9032060, 10801962. It is this involvement of zinc in DNA transcription of brain cells that provides an important means by which it plays its crucial role in brain plasticity and memory 17413652, 12450491, 19026685. Cellular level research has shown that this transcription role operates on the cytoskeleton of some brain cells, through modulation of specific transcription factors (e.g. NFAT and NF-κB) C123.

Zinc is absolutely essential for brain development. Animal studies of induced zinc deficiency during embryonic life show that the foetus suffers from decreased brain DNA and protein, impaired numbers, balance and structure of several neuronal cell types, and changes consistent with immaturity [10721938]. The CNS picture of severe zinc deficiency in rats during the period of brain growth has been described as similar to that of severe protein-calorie deficiency [7623165]. The offspring display numerous signs of CNS damage [7925188] - see Fig.Z1. In humans, pregnant women with untreated cases of the zinc deficiency syndrome acrodermatitis enteropathica produced some infants with significant brain malformations [47054].

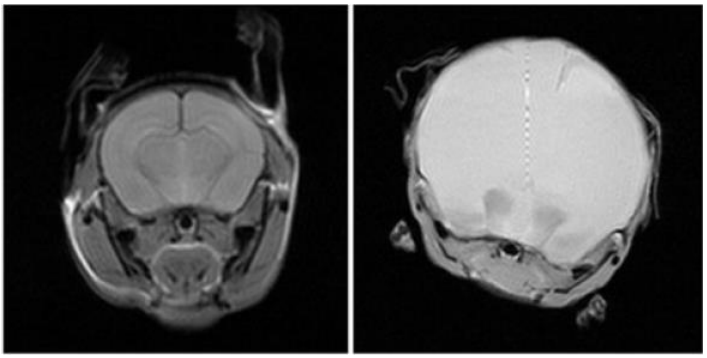

Fig. Z1. Midbrain MRI of mice: left side from a normal mouse, right side shows substantial brain malformation, and is from a mouse with the genetic abnormality seen in the zinc deficiency disease acrodermatitis enteropathica [19021533]

Zinc homoeostasis

Zinc finger proteins also play a part in what is a very tight homoeostasis of CNS zinc concentration through the blood-brain and CSF-brain barriers [19747942]. There is a further level of control of the zinc concentration within the individual brain cell, effected through a variety of mechanisms that regulate the various routes by which zinc can enter and exit the neuron. And yet another level of control brings about a marked differential concentration between the body of the neurone and the synaptic vesicle, utilising various zinc transport proteins to shuttle the zinc to where it is needed [19623531, 10801963, 9391032]. Whilst the details of those controls are beyond the scope of this review, the important thing is that they are there and that they are `strict'.

Zinc homoeostasis is absolutely crucial at all levels of the CNS. Firstly because zinc in excess can be neurotoxic, and indeed it is possible that some of its actions on the neurone life cycle may depend on that very fact (see *Zinc excess* section later). Although not fully understood, zinc concentration plays some role in the balance between neuroprotection and neuronal death, including from ischaemia, a process in which the relative concentration of zinc and calcium appears to be important [19826435].

Secondly, because some of the actions of zinc within brain cells depend on it being at a specific concentration, since neurotransmission is, after all, partly based on electrical gradients and voltage- gated membranes [12655069]. (Zinc is, in fact, an endogenous modulator of both voltage-gated and ligand ion channels [7845550]). Those electrical gradients depend not on the concentration of any one ion, but on the local ionic balance at that part of the neurone, which involves the relative concentration of several cations (e.g. sodium, potassium, calcium) [19623531, 12655069].

The amount of zinc relative to other cations is also relevant to its absorption and transport into the CNS. Although there are specific transport mechanisms that bring into the CNS each of the main essential metals (including zinc), some are less specific, and allow competitive inhibition between cations. This is also true for absorption by the gut, and the result is that the concentration of zinc, iron and copper, for example, may be interconnected, with an excess of one potentially leading to a deficiency of the other, and vice versa. It also means that deficiency of essential metals can allow increased absorption of toxic metals, such as cadmium [18389791, 11831464, 3306803, 19826435, 15173386, 7798800, 14334611, 15173386]. In addition, low zinc status can specifically affect the uptake of calcium across neuronal synaptic membranes, where this involves stimulation by glutamate [7907139]. Moreover, there is evidence that zinc deficiency can impair the integrity of both the gastrointestinal and blood-brain barriers, making it more likely that zinc deficiency disturbs the balance of other nutrients [10654621, 10654621,

One such interaction that deserves particularly close attention is that between zinc and iron. Both have in common red meat as their richest source, and a low bioavailabililty from plant sources. Hence a dietary deficiency of one is often accompanied by a dietary deficiency of the other C245, 10721906. On the other hand, it is not uncommon for supplementation to focus on only one of these two nutrients, usually iron, for example in fortified weaning foods or in pregnancy supplements. Given the potential for competitive inhibition of absorption, this creates the possibility that treating an iron deficiency with such supplements could aggravate the cognitive impairment of unrecognised and untreated zinc deficiency 10584051, 10721903, 10721906, 17237328, C228, 7925188.

Evidence of just such an effect has been reported in humans. However, in this case, it was between zinc and copper, two cations both important to cognition, whose actions are in many ways antagonistic and for which the potential for interaction is not widely appreciated 7925188. A metabolic study in which zinc and copper intakes were both substantially varied in a cross-over design found that moderately high zinc intake impaired verbal memory of healthy women when they were on a low copper diet C244.

This tightly maintained control over CNS zinc concentration has another important consequence when it comes to clinical assessment of potential cognitive impact of zinc deficiency. It means that, although dietary zinc deficiency certainly can cause brain zinc deficiency, there may be considerable sparing of the brain, such that one cannot always assume that someone with a low serum zinc necessarily also has a low brain zinc 19747942, 11831464, 11831464, 7623165.

Neurotransmission

The smaller proportion of the total CNS zinc content is found in synaptic vesicles of certain of the glutamatergic neurones in the brain, at concentrations at least an order of magnitude higher than in other parts of the CNS. Zinc achieves these high concentrations by being actively transported into the neurone and then again into the synaptic vesicle by specific zinc transporter proteins (ZIP and ZnT respectively) 19026685.

These zinc-containing neurones are referred to as *gluzinergic*, and the release of zinc from their synaptic vesicles is directly related to the nerve activity 19623531, 19826435, 11113504. The gluzinergic pathways have been extensively mapped, especially in animals - see Fig.Z2, and have been found to occur in the cerebral cortex and forebrain limbic structures, particularly the amygdala, cingulated cortex, hippocampus, and olfactory bulb 19623531, 17413652, C310. Indeed zinc-containing neurons contribute a substantial proportion of medial prefrontal cortex innervation 19623531, 17413652.

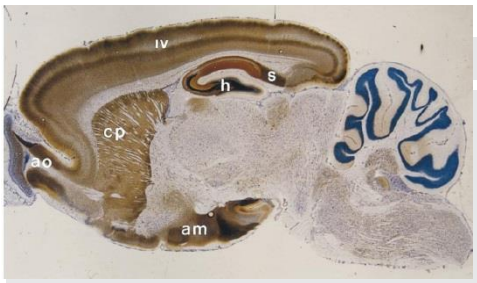

Fig. Z2. Gluzinergic neurones within the rat brain 10801962
(brown stained area)

The obvious implication is that zinc is intimately involved in the brain functions with which the corticolimbic system is involved. Those functions include attention, short-term memory, decision making and emotional processing, particularly the interaction of those elements with `higher order thinking' 19475335, 19033236, 18786735, 15784304, 9668655.

Precisely what zinc does there is still a matter under active investigation. It seems to have an important role, indeed possibly a fundamental role, in regulating cortical synaptic function, both acting directly on the post-synaptic neurotransmitter receptors and as a second messenger system 19026685, 9391032. It appears to interact with other neurotransmitters, stabilising them pre-release and influencing their clearance post-release, as well as modulating the post-synaptic receptors that bind them 9391032. This particularly applies to receptors for GABA and glutamate, and in particular the NMDA and GABA(A) receptors 19826435, 12746548, 10721938,

16321877, 18353558, 10801962, 9361293. It is zinc's action on NMDA receptors, as well as a number of other signal transduction processes, (including those that involve various protein kinases), that some believe is the ultimate cellular mechanism by which zinc is involved in brain plasticity.

It is also quite possible that zinc has its own specific neurotransmission role, independent of its actions on other neurotransmitters and their receptors 11831465, a conclusion drawn from, for example, the presence of exquisitely zinc-sensitive receptors on the other side of the synaptic gap in gluzinergic neurons 18353558.

Overall zinc is an important regulator of the excitatory and inhibitory balance of synaptic activity 16722228, 16321877, 15359010, 11831465. 19026685.

Memory

One part of the brain where zinc is particularly densely concentrated is the hippocampus 17002239, especially the hippocampal mossy fibres 1376449, 6717566, 10721938. Zinc finger proteins are involved in hippocampal nuclear transcription, and embryonically promote the formation of hippocampal neurons 12450491, 17301088. This naturally leads to the question of the role of zinc in the memory, since these mossy fibres have a crucial role in memory formation, including specifically spatial memory 11549744, C310, 12450491.

There is quite good evidence that it does have a crucial function. In animal experiments, zinc clearly has a role in hippocampal plasticity through action on the NMDA receptors mentioned above 16822975. Depleting zinc in such experiments leads to impaired synaptic activity in the hippocampal mossy fibres 224456, decreased memory test performance 19183867, 10721938, and down-regulation of certain proteins involved in memory formation 18616865. The contrary is true - zinc supplementation promotes both short-term memory, as well as specifically spatial memory C311, 20159028, 17884190. And zinc is involved in the induction of the neuronal changes associated with a process called long term potentiation, which many experts believe may be a fundamental process of mammalian learning 18304484, 17005717, 11018793, 7971146. An interesting side-light to this story is some animal data that suggests zinc supplementation may be protective against the memory impairment caused by certain toxins, such as alcohol during pregnancy 17884190, 20333752, 18793679.

Zinc deficiency

This description of normal zinc CNS physiology is a good starting point to reviewing the effects of zinc deficiency on brain function. Potential mechanisms for cognitive deficit in zinc deficiency are summarised in Table Z2.

Table Z2 : Potential mechanisms for CNS effects of zinc deficiency

Based on zinc's role with in the CNS
Protein structure (zinc finger)
Enzyme activity (catalytic site)
Neurotransmitter action (ligand gated ion channels)
Hippocampal function (mossy fibre system)
Based on extra-CNS influences on CNS
Neurotransmitter precursor production (liver)
Hormone/growth factor transport and receptor binding
Receptor binding (GH, NGF)
Hormone/toxicant metabolism (liver, testes)
Energy supply (pancreatic insulin production)
Indirect influences on CNS function
Adrenocortical activation due to starvation
Altered tissue trace metal content, especially copper
Smaller body size due to reduced food intake/growth
Selective mortality

Evidence on how zinc deficiency affects the brain has been gathered from animal experiments, from documenting known zinc deficiency syndromes and inducing them through controlled feeding experiments, observational human studies, and from randomised controlled trials.

Animal studies

Zinc deprivation causes accelerated neuronal aging in the hippocampus, associated with an excess of glutamatergic excitotoxicity. This reflects the role of zinc in excitatory-inhibitory balance [11118316]. In rats, zinc deficiency during the last part of pregnancy or the early few weeks after birth results in a small decrease in overall brain size, although proportionally less than that seen in other body organs [1195011, 1118196]. Its impact on specific elements of brain cell development is more dramatic. For instance in the cerebellum, (e.g. retarded maturation of Purkinje cells and impaired dendritic differentiation) [6488052, 6488049, 6616175, 7253806], and in the hypothalamus (leading to impaired pituitary-thyroid function) [7405879]. At a higher level of brain function, it affects animal behaviour. Rats show decreased exploratory behaviour and movement [7100289], greater susceptibility to having stress interfere with their ability to learn [12730446] and are more aggressive [564524]. Similar outcomes are seen in zinc deficient monkeys, who display decreased activity, behavioural engagement and slower response, poor visual-attention and short-term-memory task performance, either in absolute terms or in a failure to improve with time [10721905, 8030602]. They were less emotionally mature and less able to separate from their mothers [11509102].

The animal studies have been summarised by one expert as showing that zinc deficiency “affects cognitive development by decreasing activity, increasing emotional behaviour and impairing memory and the capacity to learn” [11509102].

These vulnerabilities seem to be greatest during periods of greatest growth, including pregnancy, lactation and puberty [15235141, 11509102]. Most importantly, if zinc deficiency occurred during those critical periods, it was often not reversible by subsequent zinc repletion [11509102].

Clinical zinc deficiency syndromes

Two types of clinical zinc deficiency are recognised - a chronic and an acute state.

Chronic zinc deficiency was first described as a syndrome 50 years ago, when the association was proposed between zinc deficiency and a form of severe adolescent growth retardation. This syndrome included infertility and hypogonadism, and was seen in countries (such as Iran) where traditional diets have a very high phytate content which is likely to lead to low zinc bioavailabililty [14488490, 2230544, 10721939].

This is a manifestation of chronic, though relatively moderate level of zinc deficiency [3896271]. A much more dramatic presentation that was only linked to zinc deficiency years after it was first described is the genetic disorder *acrodermatitis enteropathica*. The cause of this disease is a defective gene for a zinc carrier protein [17190629] , and although the primary symptoms are in the skin and gut, there may be mental lethargy or behavioural change [C332].

Some time later, an acute syndrome of zinc deficiency was recognised in a number of patients on artificial feeding preparations which did not contain sufficient zinc [817677, 10801941]. It had features similar to acrodermatitis enteropathica, also with some mental changes, including mental lethargy [3905080]. More light has been thrown on acute zinc deficiency, and especially its cognitive features, by a small number of human depletion studies that have been reported in the literature. One was ‘accidental’, observed in patients given a zinc chelator as treatment for an entirely different medical condition. The clinical features in that case included cerebellar dysfunction, anorexia, dysgusia and smell dysfunction as well as other “mental changes”, such as depression and psychosis [1180744].

Deliberate zinc depletion studies in healthy human volunteers have enabled more precise testing of what zinc deficiency does to human cognition [C309]. In one study, a zinc intake of 4 mg/day caused subjects to suffer impaired performance on both memory and perceptual tasks [C324]. In another study, diets of between 1 and 4 mg of zinc/day over 35 days decreased performance on a battery of cognitive and psychomotor tests, when compared to a control diet containing 10 mg of zinc. This was seen in perceptual, psychomotor, memory, spacial and attention tests [C323]. Another CNS feature commonly reported in zinc deficiency states is impairment of the special senses. This is markedly so of taste, to a lesser extent smell and, courtesy of an impact on vitamin A metabolism, is also seen in vision, particularly the rods [6349457, 11240307].

How is the CNS involved in these syndromes? In the cases of adolescent dwarfism and hypogonadism, the CNS link would partly lie in the pituitary dysfunction mentioned above as a feature of zinc deficiency reported in animal studies. Another possible mechanism for growth retardation is the impairment of the various actions described earlier as suggesting zinc can be called a 'growth nutrient', such as protein synthesis. In acrodermatitis enteropathica, a close reading of the case reports shows that depressed mood is a part of the clinical picture and one which responds to zinc replenishment [817677, 10801941, 10721938].

Human observational studies

Foetal

Although not directly cognitive, a direct possible connection between zinc and CNS development lies in the reported association between low pregnancy zinc status and various forms of neural tube defect, ranging from spina bifida to anencephaly [2980795, 6657709, 19430086, 18309769, 16536302, 15501379, 3895882]. A ready explanation lies in animal study data showing that zinc and zinc finger proteins play an important role in the embryogenesis of neural tissue [18701545, 17490632, 15207846]. There is also a possibility that the link with NTD arises from an influence of zinc on folate metabolism [2183337], or on levels of other minerals such as copper [19430086]. No human clinical trials have been done involving zinc supplements alone to prevent NTD, but it has been given as part of a broader multivitamin supplement whose main focus was folate. In a randomised, controlled trial of 466 women with a previous NTD offspring, this combined supplement reduced the risk of recurrence [11247198].

Whether the link to NTD applies to zinc status only at the extremes or also in the `mid-range' is not clear. Most of these reports were from countries with distinctly low bioavailable zinc intake. In relation to Western countries, results are mixed - in some studies, associations have been found [10535785, 2466480, 6466580], but in others not [7935120, 8399013, 1342805]. It should be noted that there have also been reports of associations with higher levels of urine and hair zinc [3880387, 7424808, 7424808], and with very high serum zinc [7424808]. This suggests some abnormality of zinc distribution might be involved.

Paediatric

Serum zinc in the last 6 months of pregnancy was associated with lower Bayley motor test scores at 6 months of age in the infants of Egyptian mothers [7942587]. In a group of American elementary school children there was a positive correlation between hair zinc and both reading ability and coherence of frontal lobe EEG [6597699]. Changes in EEG were also seen (in its response to hyperventilation) in adult subjects with low zinc red cell levels [891456], and there was a correlation between EEG power in the β band during cognitive tasks and plasma zinc in aged subjects [2360555]. There was a correlation between plasma zinc and EEG activity in some of the subjects involved in a metabolic study of zinc depletion [C326,10721907]. There was no link between serum zinc and visuomotor ability in healthy Argentinian 4-10 year olds [17916959].

Adults

Ethiopian women with zinc deficiency (serum level < 7.6 µmol/l) scored significantly lower in a test of abstract reasoning than those without [19190668].

Elderly

Plenty of observational studies have shown the elderly to be a high risk group for zinc deficiency (e.g. [19657552, 15003923, 10801945]). Not nearly as many have reported on the cognitive consequence. The more informative studies reported on blood zinc status, for example the association of lower serum zinc (adjusted for age) with more senile plaques in elderly nuns [8595180]. There was some link between marginal zinc deficiency (serum zinc $\leq$ 11.0 µmol/l) and worse psychological test scores in Greek subjects aged between 60-84 years [16969711]. The association of plasma zinc with EEG power during cognition in aged subjects has already been mentioned [2360555]. In a cross-sectional study of 1,451 older community based Americans (average age 75 yrs) serum zinc was only positively correlated with scores on a single of several tests of cognitive function [18165841]. The baseline values of a zinc intervention trial showed no consistent correlation between serum zinc and cognitive test scores [17010236], nor was their one in an Italian study of older subjects with some degree of cognitive impairment [15207438]. A study purported to find `zinc status' linked with more depression in a group of elderly Europeans, but the measure of zinc status used - serum albumin - hardly passes muster as a specific indicator [17317461]. There was no relationship between plasma zinc and cognitive test scores in a study of elderly Chinese [18559640].

A number of studies reported on dietary zinc intake. There was no correlation between cognition and use of antioxidant supplements, including those containing zinc, in a study of community based American elderly [9663402]. Just such a protective association was found in another such study, this time

prospective 15555461. Obviously neither gives a precise assessment of zinc's role in the findings! Differences between zinc content of the communal drinking water used by two Chinese communities was found not to be correlated with the cognitive scores of the elderly citizens living in those communities 10791564. There was some association between zinc intake (along with many other nutrients) and a Mental Status Questionnaire score in a group of elderly Spaniards 9322553. Frankly, given the potential for confounding in
these study designs, (as some of those study authors themselves acknowledged 9322553, and see the section on *Confounding* below), these results are of only marginal relevance to the subject at hand.

Other CNS diseases

There have been observational studies of zinc in relation to specific psychological or neurological disorders. These have been mostly cross-sectional (i.e. case-control). Although this review concerns normal cognition, some of these studies are worth mentioning in so far as the associations could reflect in some way zinc's role in normal brain function.

For example, there are quite a few studies showing lower zinc status in children with *attention deficit disorder*, with a few reporting correlation between zinc levels and symptom severity or responsiveness to conventional treatment 16190793, 19176735, 10933121, 2269593. It has been suggested that this may be because of imbalance of neurotransmitters dopamine and serotonin, in so far as zinc is involved in the melatonin production which in turn regulates dopamine function, and in bioactivation of vitamin B_6 which in turn is required to convert tryptophan to serotonin 19176735. These ideas remain, however, in the realm of theory.

The same applies to reports of low zinc levels in *depression* and that zinc levels increase after anti-depressive therapy 16382189, 16358590, 9662732, 2291414, 16491668. Some researchers believe this is due to a zinc-related alteration of glutamatergic and/or GABA neurotransmitter function, requiring some intervention at the NMDA receptor 9662732, 17439925, 11370292, 11490890, 16382189. A more recent theory that zinc is relevant to depression because the illness represents a CNS inflammatory disorder remains speculative 20156515.

There is a single report that patients with dyslexia had lower sweat zinc than controls C330. There have been isolated reports of lower zinc status in *epilepsy* 1907237, *autism* C232, *mental retardation* 3196075 and childhood *anorexia nervosa* 8444822, the latter being of interest because of the impact of zinc deficiency on the special senses of taste and smell. At the same time, it should be acknowledged that the risk of confounding in such studies is high, since people with these conditions are quite likely to be eating poorly overall.
The same can be said about the many studies which have reported changes to zinc status in *Alzheimer's disease*. For example, lower serum or plasma zinc 20569929, 19911117, 18997297, and reduced levels of brain zinc in some areas with higher levels of zinc and zinc transporter proteins in others, linked to the amyloid deposits that are characteristic of this disease 19276540, 18639746, 9164672, 8400761. These findings have been considered important clues not just to understanding Alzheimer's disease, but also as casting light on zinc's physiological function in neuronal cell death, the balance between that function and neuroprotection, between excitation and inhibition, between zinc and other metals (such as copper and aluminium), overall zinc homoeostasis within the CNS, and how all of this changes with brain aging 19826435, 18078729, 16522327, 15927345, 16308484, 16308478, 12505647, 9164672, 19276540.

Another medical condition which researchers believe might offer insight into the balance of zinc's actions in the brain is *epilepsy*. There is some evidence of lowered serum and CNS zinc in febrile convulsions and epilepsy 18795906, 17873242, 7492199, 10365598, 8789769, 7114883, 6816908, 3197701, but a review of the literature found it overall to be inconsistent (leaving aside the effect of anticonvulsants in decreasing them further!) 16775802. The insights into normal brain function lie in the balance between excitatory and inhibitory actions of zinc on neuronal activity, how zinc is involved in responding to neuronal insult, and in the role of the hippocampal mossy fibres in augmenting hippocampal activity, (which in the case of epilepsy, can lead to temporal fitting) 11050320, 19623531, 14584819, 10999528, 11831464. The spectre has also been raised that excessive zinc supplementation might aggravate epilepsy 18468689.

The clinical trial evidence on the use of zinc supplements to prevent or treat these CNS disorders is discussed in the appropriate section below.

Confounding

One issue that has to be taken into account with all these observational studies is the potential for confounding. There are a number of possible confounding factors 10721907. One that we have mentioned earlier is the impact of underlying illness on zinc status. For instance, when impaired cognition is the

cause, and not the effect, of the zinc deficiency because the patient with impaired cognition is not eating well.

Another already touched upon is effect of interactions between zinc and other nutrients, particularly minerals, such as copper, magnesium and iron, and also with so-called heavy metals (such as cadmium and lead) 15173386 , 12655069. For example, an association between zinc and brain function may actually be due the coexistant changes to lead, copper or iron status 18035344, 7082716, 16410985. A good example is the dyslexia study referred to above, where the low sweat zinc was accompanied by elevated copper, lead and cadmium C330. Another example where the pattern of lower zinc, higher lead and cadmium was seen was in the placental tissue of children with reduced head circumference C331.

One study of American preschool children did try to separate out these interacting influences. The authors calculated that zinc and iron status together accounted for 25% of the variance in the children's verbal intelligence scores, zinc status alone explained 39% of the variance in teacher ratings of boys' anxiety, whilst lead levels accounted for 20-25% of the variance in teacher ratings of girls' sociability and classroom competence 17197281. There are limitations in such statistical manipulation, but the main lesson is clear - that these factors can coexist and co-influence cognition.

There is another source of confounding that is probably much more relevant than the above factors, particularly in human observational studies. This is the influence of the poverty in which many zinc deficient people live, and unsurprisingly therefore from which many of the subjects in these studies came 9701161, 12730451. Low socioeconomic status often brings with it poorer general lifestyle and health, poorer overall nutrition, a higher level of stress and psychological impoverishment and more dysfunctional parenting 10721907, 9701161. The preschoolers study referred to above, as well as dissecting the co-influence of iron and lead, also tried to separate out the interaction of parenting style on the cognitive outcomes 19267294.

These diverse effects of being poor can affect cognition directly in a great many ways. This is the subject of a huge literature that is not appropriate to go into here. (The topic of general undernutrition, however, is covered in the relevant chapter of this review). They can also affect it less directly by triggering more complications during pregnancy, including placental dysfunction, pre-eclampsia, prematurity, lower birthweight and small for gestational age, all of which in turn can cause damage to the baby's vulnerable developing nervous system 8494261, 9707701, 10721938. The complex web of circumstance thus weaved can be very hard to separate out in observational research 10721907 .

Human clinical trials

For these reasons, the most important evidence we have comes from randomised, placebo-controlled human intervention trials of which there have been several dozen. Some used zinc alone, whilst others combined it with other nutrients, most commonly iron. They are summarised in Table Z3, which appears at the end of this section.

Paediatric trials

Zinc was given antenatally to Peruvian pregnant women and increased the foetal heart rate variability and foetal movements, both of which have been proposed as measures of foetal neurodevelopment 15118650, 9988823, 9022256, 11509102, (although not everyone agrees with this assumption 11509097). Interestingly, the results of a follow-up ECG at 4½ years of age on a sub-set of those children has just been reported. They still show signs of enhanced autonomic function, in terms of greater heart rate variability and respiratory sinus arrhythmia C327. Increased head circumference in the newborn, which suggests greater brain size, was found in two trials of zinc supplementation given to pregnant women. In one of those trials, in Iranian women with a history of preterm delivery, researchers reported an increase in head circumference of 1.3 cm, compared with placebo-treated women 19658043. In the other, involving African-American women with sub-optimal zinc status, there was an average increase of 0.7 cm 7629954, but no significant differences in test scores for mental and psychomotor development that were administered to these children when they were followed up at 5 years of age, comparing those whose mothers had zinc vs placebo 12791632. Nor was there any impact on Bayley scales of infant development or behaviour scores when the infants of Bangladeshi mothers who were given zinc during pregnancy were reviewed at 13 months of age 12147372.

The cognitive outcome of giving zinc supplements to children after birth seems to be somewhat better than those antenatal trials, although the results by no means point one way. For example, zinc supplementation for 8 weeks from immediately after birth improved infant behaviour scores at 12 months

follow-up in low birthweight Brazilian infants, but not in Bayley developmental scores, compared to placebo 9537305. Zinc was given to neonates from poor Chilean families for a year. Although their mean psychomotor and mental development scores did not differ from those of the placebo group, a smaller percentage of them had low scores 11174621.

In another trial of very low birthweight Canadian infants, 3 months of zinc supplements resulted in higher maximum motor development scores than placebo 8350219. Generally undernourished Jamaican children (aged 9-30 months) given zinc improved their developmental quotient and hand-eye coordination, but only in those who also received psychosocial stimulation as part of the randomised intervention 16087985. Guatemalan infants (6 to 9 months old) treated with zinc supplements for 7 months had better scores for motor (sitting up and playing) and emotional (crying and whining) observations than placebo 9202087. On the other hand, elemental zinc given to one month old Bangladeshi infants actually resulted in a slightly but significantly worse Bayley mental development score 11522564, something the researchers postulated may have been due to the kind of nutrient imbalance that is implied by the mineral interactivity discussed earlier.

In an older age group of children, extra zinc was taken by Guatemalan primary school students for 25 weeks, but both they and the placebo group had similar improvement in their cognitive test scores 8438768. There was no impact on attention span from zinc (10 mg/day) supplementation of Canadian boys aged 5-7 years 2729165. Zinc supplementation given to Indian adolescent girls for 10 weeks resulted in improvement in several tests of memory and other cognition, and this was similar whether taken as food or as supplementary tablet 20368377. Zinc gluconate at a dose of 20 mg/day administered to 209 American schoolchildren (in the 7th grade) for 10 weeks resulted in improved performance in visual memory, word recognition and target detection tasks, compared with placebo C226.

There have been a reasonable number of randomised, controlled trials in which a mixed nutrient supplementation included zinc and which resulted in a significant impact on cognitive outcomes. Multinutrient supplements given to Indian schoolchildren enhanced their memory scores 20533221, and the level of activity and movement undertaken at play by Indian children in their second year of life 8951265. A multinutrient package (with zinc but excluding iron or calcium, in order to avoid mineral absorption competition) administered to two different samples of Chinese schoolchildren (6-9 years old) from poor families improved their scores of neuropsychological performance, more so than zinc or micronutrients alone 9701162, 9176834, and a similar result was obtained in a study of the same design on Mexican-American children C329. The greatest response in all three of these trials from the same research group was obtained with a supplement providing zinc at 20mg/day along with “potentially limiting micronutrients” 10721938. An iron-zinc combination improved motor development and exploratory behaviour in impoverished Bangladeshi infants 15447897. Adding zinc, iron, iodine and vitamin A to school lunches of primary school children in Thailand improved short-term cognition 18541560.

On the other hand, in some trials it has not had a beneficial impact on cognition. Zinc-only and zinc plus iron supplements had no positive effects on psychomotor development in a trial on 680 Indonesian infants, whereas iron alone did 15321815. There was no effect on Bayley developmental scores from adding zinc to a multinutrient supplement for small for gestational age Indian infants when given daily from 30 days to 9 months of age 15121945. Nor was any cognitive improvement found when zinc was part of a supplement together containing iron and folate given to infants from Nepal 20484548, or when zinc and iron were given to school-children living in lead-affected areas of Mexico 16510631, 16291354. A randomised trial of zinc, iron and folic acid in Nepali infants between 4 and 16 months of age failed to show any effect on language acquisition, but it was discovered that the active and placebo intervention groups differed in potentially important variables at baseline C181. Another trial from that research group involving the same supplement combination given to infants showed some inconsistent, non-statistically significant impacts on executive function tests C180.

Turning to therapeutic trials in CNS related diseases, two from Iran and Turkey reported improvements in symptom scores amongst children with attention deficit disorder after receiving zinc sulphate for 6 and 12 weeks respectively 15070418, 14687872. In a small trial in adolescent anorexia nervosa patients, zinc supplements resulted in a decrease in the level of depression and anxiety 3312133 (and another trial did not report on cognitive outcomes 8199605)

Adult trials
There have been fewer trials on adults than on children. When 15 or 30 mg of zinc was given to British adults of middle aged and above (ZENITH study), the cognitive outcomes were mixed. A measure of spatial memory improved, but a measure of attention deteriorated, compared with placebo [17010236]. A rather unusual perspective on the impact of zinc supplements on mood was provided by a trial in elderly European subjects, in which the impact on stress scores was significantly greater than placebo, but only in those with a specific polymorphism in the gene for the inflammatory compound interleukin-6 [18341424]. Zinc supplements given to adult women (age not stated!), along with multivitamins, in a pilot Japanese trial, produced a greater improvement in anger and depression scores, but not in other mood indices, compared with multivitamins alone [20087376]. In a small pilot trial of women with non-anaemic iron deficiency, zinc (30 mg/day) and/or iron brought about improvements in both verbal and visual memory, which were not seen in those just taking a multinutrient supplement without zinc or iron [1297799, C322].

Used therapeutically, zinc given together with the conventional anti-depressants enhanced the speed and extent of the therapeutic response in adult depressives [19278731, 14730113]. There was no effect on cognition from taking zinc for around 7 years, as part of a package of antioxidants and copper given in a trial in 2,166 older American subjects, the main aim of which was to prevent macular degeneration [15534261]. When given to schizophrenics in a small trial, the patient's EEG pattern moved towards normal [674538].

Conclusion
Overall, the trend was for positive cognitive outcomes. This was reported in 28 of the 41 trial results listed in Table Z3, (compared with 10 null, 2 negative impact and 1 mixed results). However, the variation in population sample, form and dose of supplement, outcome measures tested and general methodology between these trials does not allow us to reach any convincing conclusion about the value of zinc supplementation in improving cognitive function. This is even more so given that in many of these trials, despite in most cases testing baseline and post-intervention zinc status, did not present the results categorised by initial zinc status. Almost none of the trials specifically concentrated on zinc supplementation in clearly zinc deficient subjects.

What is noticeably missing from the existing clinical data set are long-term trials in children who have suffered a period of initial zinc deficiency, demonstrating to what extent any cognitive deficits have been made up through that supplementation. Although there certainly are trials that showed higher risk children improved cognitive test scores after zinc supplements, they do not show that they have improved to the extent of overcoming the original deficits, which in any case were usually not well documented to begin with.

In regard to otherwise healthy adults and the elderly, the trial evidence is even scanter. There are so far only a couple of human trials suggesting that replenishment will overcome this.

Table Z3: Randomised trials of zinc supplementation with cognitive outcomes.

PMID	Country	Sample	n	Intervention	Duration	Outcome measure	Result
Trials in children							
19658043	Iran	Pregn	84	Zn	From 12-16/42	Head circum	+
7629954	USA	Pregn with low Zn	580	Zn	From 19/42	Head circum	+
12791632	"	Chlildren (5 yr) from above study	335	"	"	Various cognit tests	NS
12147372	Bangladesh	Pregn	559	Zn	From 16/42	Mental and psychomotor develop	-
9988823	Peru	Pregn	55	Zn +/or Fe/folate	During pregn	Foetal heart rate variability, movement	+
15118650 C327	Peru	Pregn from low income household	242 105	Zn + Fe/folate	From 10-16/42	Foetal heart rate variability Children assessed again at age 4½ yrs	+ +
11247198	India	Pregn with prior NTD baby	466	Zn + folate + multi	1 mo pre- to 3 mo post-concep.	Recurrence rate	+
11174621	Chile	Neonates from poor families	102	Zn	12 mo	Psychomotor and mental development	+*
9202087	Guatemala	Infants	85	Zn	7 mo	Sitting and play activity	+
9537309	Brazil	Low birthweight term infants	134	Zn	8 wk	Bayley Scales of Infant Development	NS
8350219	Canada	Very low birthweight infants	52	Zn + formula	6 mo	Griffiths developmental assessment	+
15121945	India	SGA infants	200	Zn + multi	8 mo	Motor develop, oriemtation/engagement	NS
11522564	Bangladesh	Infants (1 mo)	301	Zn	5 mo	Bayley Scales of Infant Development	+
15447897	Bangladesh	Infants (6 mo)	221	Zn +/or iron +/or multi	6 mo	Motor develop, oriemtation/engagement	+
15321815	Indonesia	Infants (6 mo)	680	Zn +/or iron	6 mo	Psychomotor development	NS
20484548	Nepal	Infant/toddlers (1-36 mo)	3,264	Zn + Fe/folate	Until walking	First walking age	NS
C180, C181	Nepal	Toddlers (4-16 mo)	569	Zn +/or Fe/folate	1 yr	Language acquisition, execut function	NS
8951265	India	Toddlers (12-23 mo), poor family	93	Zn + multi	30-120 d	Play activity	+
16087985	Jamaica	Children (9-30 mo), undernourished	114	Zn	6 mo	Mental Development	+
18541560	Thailand	School children (5-13 yrs)	569	Zn + Fe/iodine/ Vit A	31 wk	Visual recall test	+
20533221	India	Children (5-18 yrs)	1,502	Zn + multi	9 mo	Memory, attention	+
2729165	Canada	Children - boys (5-7 yrs)	60	Zn	12 mo	Attention span	NS
9701162	China	School children (6-9 yrs)	740	Zn +/or multi	10 wk	Neuropsychologic performance	+
9176834	China	School children (6-9 yrs)	372	Zn +/or multi	10 wk	Neuropsychologic performance	+

PMID	Country	Sample	n	Intervention	Duration	Outcome measure	Result
C328	USA	School children (6-9 yrs) of Mexican-American ethnicity	240	Zn +/or multi	10 wk	Neuropsychologic performance	+
C226	USA	School children (7th grade)	209	Zn	10 wk	Cognitive tests + psychosocial function	+
8438768	Guatemala	School children (mean age 7 yrs)	162	Zn	25 wk	Cognitive score	NS
16510631/ 16291354	Mexico	Lead exposed school children	602	Zn +/or iron	6 mo	11 cognitive tests, behaviour	NS
15070418	Iran	ADHD children	44	Zn + ADHD drug	6 wk	Parent/teacher rating	+
14687872	Turkey	ADHD children	400	Zn	12 wk	Teacher rating	+
3312133	USA	Adolescents with anorexia nervosa	?	Zn	?	Depressive symptoms	+
20368377	India	Adolescent girls	180	Zn: food and supp	10 wk	Cognition (reacn time, visual memory, Raven)	+
Trials in adults							
20087376	Japan	Adult women	30	Zn	10 wk	Mood	+
C244	USA	Adult women	23	Low/high Zn/Cu	Crossover x 90 d	Verbal memory	-
1297799/ C322	USA	Adult women with iron defic.	34	Zn +/or iron +/or multi	8 wk	Memory (verbal and visual)	+
19278731	Poland	Adults with depression	60	Zn + conventional antidepressant	12 wk	Antidepressant response	+
14730113		"	14		"	"	+
Trials in elderly							
18341424	Europe	Elderly	97	Zn	48 d	Stress and other psychol measures	+
17010236	UK	Middle age/elderly (55-87 yrs)	387	Zn	6 mo	Memory, attention	Mixed

Duration: of intervention. **Outcome measure**: refers to cognitive measures only
Result: + = better, NS = no signif diff, - = worse outcome for zinc intervention.
Where only one measure had significant result, that is the one listed
***** no diff in means, diff in % with low scores

Zinc excess

The other side of the coin is zinc excess. Zinc has a definitely neurotoxic aspect, for a variety of reasons. These include the fact that it can be both pro- and antioxidant, and deficiency and excess can each lead to redox stress. Indeed, this may be part of the physiological role that zinc plays in neuronal cell death as part of the natural neurone life cycle and the `rewiring' involved in brain plasticity, memory and learning [16308485]. The neurotoxic side of zinc may also be involved in natural aging, and in pathological process. For example, there is evidence that local zinc mobilisation and release occurs in Alzheimer's disease, amyotrophic lateral sclerosis, epilepsy, cerebral ischemia and brain injury [16308485, 19623531, 19826435, 19826435, C320].

Hence the overriding message that comes out of the literature is of the importance of zinc balance to healthy function within the CNS. This is highlighted in Fig.Z3, taken from a recent review [19623531]. A natural implication of this is the caution that should be applied in uncontrolled supplementation with zinc, in the absence of good clinical indications that a zinc deficiency is present. Particularly bearing in mind the relative lack of sensitivity of conventional laboratory tests to determine zinc status, not to mention the almost complete lack of means to assess CNS zinc in a practical way in a real life clinical situation.

Caution is warranted not only because of the potential for zinc toxicity, but also because of the possibility of disturbing the balance of other nutrients, as has been discussed earlier. On that basis, naturally balanced sources of zinc, such as animal foods, have much to commend them in dealing with zinc deficiency.

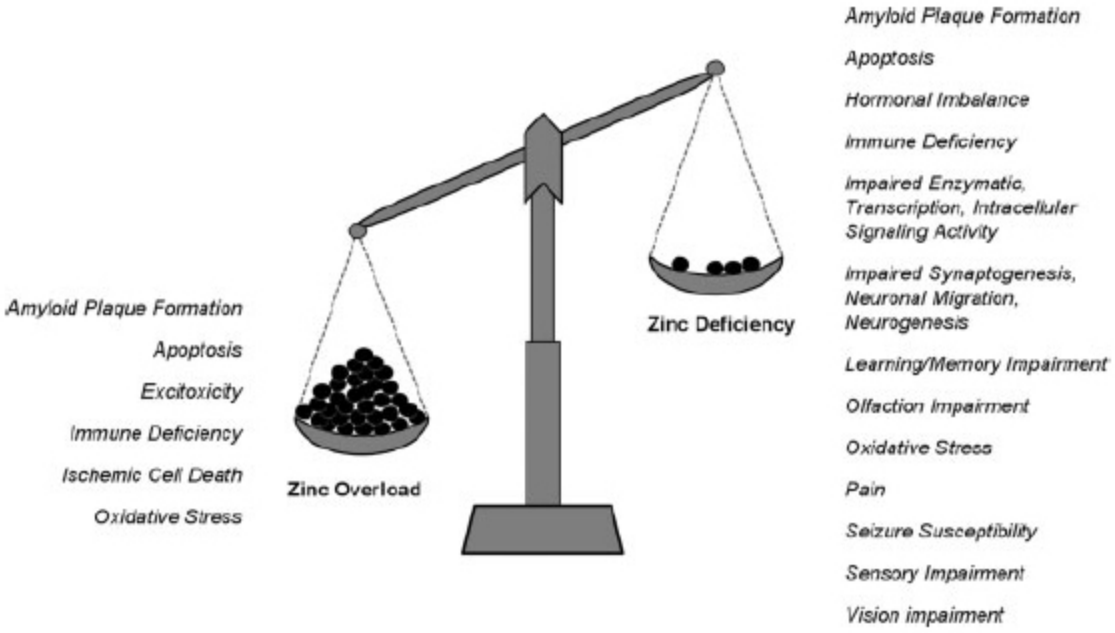

Fig. Z3. Zinc excess and deficiency are both associated with CNS pathology [19623531]