Omega 3 fatty acids and the ageing brain

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ILSI and The Omega 3 Centre, Workshop
Key points

- Blood vessel (vascular) health is very important for neural health.
- Brain needs blood to supply glucose for its fuel.
- Vascular dementia is the second most common form of dementia.
- Blood vessels become damaged by the amyloid in brain in Alzheimer’s disease.
Is it realistic to ‘reverse’ these dramatic changes?

In the Alzheimer's brain:

- The cortex shrivels up, damaging areas involved in thinking, planning and remembering.
- Shrinkage is especially severe in the hippocampus, an area of the cortex that plays a key role in formation of new memories.
- Ventricles (fluid-filled spaces within the brain) grow larger.
Key topics

- Ageing and loss of neurones in dementia
- Neural connectivity
- Brain and omega 3 connection
- DHA promotes synaptogenesis
- Brain and fuel supply
- Blood supply and neural health
- Dementia
- Alzheimer’s disease
- Can it be reversed or prevented

- Animal studies on improving synaptic function
- Human studies on a medical food drink in mild AD
- Studies on omega 3 in elderly subjects
Ageing and the brain

- Brain is the most complex organ in the body,
- The human brain has 100 billion neurones and each of these has projections (dendrites) and these form connections with other neurones at a junction point (the synapse).
- There are 10,000 billion synapses in the human brain ($=10^{13}$).
- In Alzheimer’s disease, hundreds of thousands of neurones and synaptic connections are lost daily.
Increasing neuronal connectivity with age

http://www.theemotionmachine.com/mindfulness-and-neuroplasticity

10^{11} neurones and 10^{13} synapses in adult brain
The **omega 3 fatty acid, DHA**, is found in the neuronal cell membranes in the phospholipids (PS, PE & PC).

Recently, it has been shown that a DHA derivative promotes the formation of synapses (DHA-ethanolamide), *Kim H-Y et al 2011*. 
DHA promotes neurite outgrowth in hippocampal neurones

**Fig. 2** Effect of DHA on the total neurite length per neuron after culturing with DHA for 6 days. (a) Camera Lucida drawings of representative neurons. All data represent the average of 40 neurons per condition.

New DHA metabolite discovered, DHA-ethanolamide, that promotes synaptogenesis, Kim H-Y et al 2011
It is not this simple... DHA in food → brain

- Brain is thought to be supplied with DHA from the blood, which in turn is largely derived from DHA in food.
- Therefore, low/high diet omega 3 might lead to low/high plasma DHA, but it is unlikely to influence brain DHA levels in the short term.
- Animal studies suggest that brain DHA levels are really stable. For example, it takes many weeks to deplete brain DHA to 50% of control levels on a diet almost devoid of omega 3 FA.
What is the energy source for brain function?

- Brain uses glucose from the blood as its primary fuel.
- This glucose is metabolised and produces ATP (the energy source that drives brain function),
- Brain glucose metabolism accounts for 20% of total energy use by the whole body (it rises as brain works harder),
- Thus, **blood supply** to the brain is fundamental for adequate brain function.
Extensive blood supply

Therefore, blood vessel (vascular) health is very important for neural health.

There is a very strong association between cardiovascular disease and depression.

Vascular dementia is the 2\textsuperscript{nd} most common form of dementia.
Nutrition and neural health

- Continuing this theme, since nutrition is strongly associated with blood vessel and CVD health, it follows that there will inevitably be a connection between high quality nutrition and neural health mediated by the health of neural blood vessels.

- Therefore, ageing and CVD and brain function are connected by the relationship between nutrition and blood vessel health (which nutrients?).

- B-vitamins (folate, B12), some antioxidants, and omega 3 fatty acids.
For people aged 65 and over, **dementia** is the second leading cause of overall burden of disease and the leading cause of disability burden in older Australians.

Dementia is a progressive deterioration in a person's functioning.

The most common cause is Alzheimer's disease but there are other causes including Parkinson's disease and Huntington's disease.

Common early symptoms include memory loss, confusion, personality changes, apathy and withdrawal.
Mental health issues

- An estimated 298,000 Australians had dementia in 2011, of whom 62% were women, 74% were aged 75 and over, and 70% lived in the community.
- Dementia was the third leading cause of death in 2010 (accounting for 6% of all deaths), with an average of 25 people dying from dementia every day that year.
- Twice as many women as men died from dementia (6,083 and 2,920 respectively).
Mental health issues

- Dementia poses a substantial challenge to health, aged care and social policy.
- Based on projections of population ageing and growth, the number of people with dementia will reach:
  - almost 400,000 by 2020, and
  - around 900,000 by 2050.
Mental health issues - Alzheimer’s disease

- The number 1 neurological disease, first described in 1907.
- Genetic/inherited forms account for <10% of AD, with remainder of unknown cause,
- Widespread and significant neuronal loss and loss of dendrite synapses (branching/connections to other neurones),
- **Five areas of brain** show most pronounced loss of cells – hundreds and thousands of cells lost/day,
- Anatomical evidence of massive changes with histological evidence of abnormal filaments (tangles), plaques contain beta-amyloid in extracellular space and blood vessels become damaged by the amyloid in brain; rupture of blood vessels leading to cerebral hemorrhage. Also accumulation of metals (Al) in brain.
Mental health issues - Alzheimer’s disease

- Behavioural changes – loss of initiative, depression, faulty judgement, massive memory loss, loss of higher order function (jokes), mood disturbances, severe memory loss, long-term memory gone.

- Mostly there is no cure; can only treat symptoms.

Risk factors - Decrease risk

- Apolipoprotein E2/E2 allele gene variant
- Fish intake (not necessarily supplements)
- Maintaining normal weight
- Taking foods high in antioxidants (food variety)
- Exercise – hippocampus can make new neurons and exercise increases the # of neurones in this area.

Continuing mental challenges throughout life
Mental health issues - Alzheimer’s disease: Risk factors

**Risk factors – Increase risk**

- Age: 1 in 8 if >65y; and 1 in 2 if >85 y
- Apo E4/E4 allele = gene variant
- Head injury
- High fat diet, elevated plasma cholesterol levels, obesity
- Atherosclerosis, diabetes, hypertension
- Smoking
- Diagnosis of mild cognitive impairment
- HRT

Most of these risk factors are the same as for CHD, stroke, heart attack. AD & CHD are co-morbid diseases.
Mental health issues - Alzheimer’s disease: Risk factors

The Nun experience (Tyas et al, Age and Ageing 2007)

- They agreed to donate their brains for examination after their death.
- Lifestyle, food simple, exercise, continuous learning.
- Some of the brains of the nuns looked like they originated from people many years younger.
- Lesson is that normal ageing does not have to be associated with major cognitive decline.
- Only those nuns whose brains showed evidence of a cerebral infarct had AD based on autopsy
- Nuns with least learning during life had most AD
Is it realistic to ‘reverse’ these dramatic changes?

In the Alzheimer's brain:

- The cortex shrivels up, damaging areas involved in thinking, planning and remembering.
- Shrinkage is especially severe in the hippocampus, an area of the cortex that plays a key role in formation of new memories.
- Ventricles (fluid-filled spaces within the brain) grow larger.
**Major loss of neurones**

- Major loss of neurones in the neocortex – higher order neuronal cells – that degenerate,
- Loss of neurones is massive leading to cortical atrophy seen at autopsy.
- Can still see & hear, but **thinking** is a challenge,
Prevention or reversal – what data is available?

- Wurtman et al. have studied treating animals with synaptic membrane precursors (phospholipid precursors - including uridine, choline and DHA) which can increase brain phosphatide levels, synaptic proteins, neurite outgrowth and the formation of dendritic spines (Nutr Rev 68:S88-101, 2010).

- Follow-up studies with uridine and DHA showed increases in synaptic membranes, increased neurotransmitter levels and enhanced performance in tests of learning (Morris water maze) in rats in impoverished environmental conditions.

- These studies lead to several clinical trials......
Medical food improves memory in mild AD patients (Souvenaid 1)

- Efficacy of medical food in mild Alzheimer’s disease, an RCT.
- A total of 225 drug-naïve AD patients participated in this randomized, double-blind controlled trial (multicentre study).
- Patients were randomized to active product, Souvenaid, or a control drink, taken once-daily for 12 weeks.
- Primary outcome measures were the delayed verbal recall task of the Wechsler Memory Scale-revised, and the 13-item modified Alzheimer's Disease Assessment Scale-cognitive subscale at week 12.
Nutritional composition of drink

Component Amount per daily dose (125 mL at breakfast in tetrapak)

- EPA 300 mg
- DHA 1200 mg
- Phospholipids 106 mg
- Choline 400 mg
- UMP (uridine monophosphate) 625 mg
- Vitamin E (alpha-TE) 40 mg
- Vitamin C 80 mg
- Selenium 60 mg
- Vitamin B12 3 mg
- Vitamin B6 1 mg
- Folic acid 400 mg

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; TE, tocopherol equivalents.
*Souvenaid contains the above ingredients plus other vitamins, minerals, trace elements and macronutrients. The control lacked the above listed nutrients.
Supplementation with a medical food (including phosphatide precursors and cofactors) for 12 weeks improved memory (delayed verbal recall, p=0.021) in mild AD patients. This proof-of-concept study justifies further clinical trials.
The Souvenaid II study was a 24-week, randomized, controlled, double-blind, parallel-group, multi-country trial to confirm and extend previous findings in drug-naïve patients with mild AD (n=259). Patients were randomized to receive Souvenaid or an iso-caloric control product once daily for 24 weeks. The primary outcome was the memory function domain of the Neuropsychological Test Battery (NTB). The NTB memory domain Z-score was significantly increased in the active versus the control group over the 24-week intervention period (p = 0.023).
Mean change from baseline in the Neuropsychological test battery memory composite score, at 24 weeks, $p=0.023$ between Active and Placebo

- **Souvenaid** was well tolerated and improved memory performance in drug-naïve patients with mild AD.
- EEG outcomes suggested that Souvenaid had an effect on brain functional connectivity, supporting the underlying hypothesis of changed **synaptic** activity.
Some studies in dementia

- **Schaefer et al 2006**: Top quartile of plasma DHA was associated with significant risk reduction for dementia in the Framingham heart study (n=899 followed for 9.1 y),
- **Freund-Levi et al 2006**: n-3 FA treatment in mild to moderate AD did not delay decline in AD (n=204, 6 mo),
- **Barber-Gateau et al 2007**: Frequent consumption of fruits and vegetables, fish and n-3 oils may decrease risk of dementia & AD, especially among APOE4 non carriers (n=8085, dietary patterns),
- **Kotani et al 2006**: DHA and AA treatment for 90 days (RCT); no effect on memory or attention for AD, improved immediate memory for MCI patients.
Omega-3 Supplement intake is associated with less Cognitive Decline in Elderly Chinese

- Design: Prospective cohort study
- Participants: 1,475 healthy Chinese adults ≥ 55 years old in urban Singapore
- Measurements:
  - Daily omega 3 PUFA supplement intake and fish intake, at baseline
  - Cognitive function: Mini Mental State Exam (MMSE) at baseline and 1.5 y later
  - Odds ratios of association between n-3 PUFA supplement intake and cognitive decline calculated in logistic regression models.

### RESULTS: 63% risk reduction

<table>
<thead>
<tr>
<th>Logistic Regression Model</th>
<th>OR(95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.38 (0.16-0.88)</td>
<td>0.023</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.37 (0.16-0.87)</td>
<td>0.024</td>
</tr>
<tr>
<td>Excluding respondents with cognitive impairment (MMSE &lt;24) at baseline</td>
<td>0.36 (0.15-0.85)</td>
<td>0.020</td>
</tr>
<tr>
<td>Excluding respondents with cognitive impairment, diabetes, stroke and cardiac disease</td>
<td>0.23 (0.07-0.75)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

There was no association of fish consumption and cognitive decline!

**MIDAS: Memory Improvement with Docosahexaenoic Acid Study**

**Goal:** Evaluate the effects of algal DHA on cognitive outcomes in healthy elderly (≥55 yrs) with a mild memory complaint (age-related cognitive decline)

**Design**
- Randomized, double-blind, placebo-controlled, parallel, multi-center
- 465 subjects with subjective memory complaint
- **Oral dose:** 900 mg/day Algal DHA or placebo (corn/soy) for 24 weeks.
- Main outcome measures:
  - Cognitive function: PAL test - a visuospatial learning and episodic memory test
  - Heart rate

MIDAS: Algal DHA Improves Memory Function in Age-Related Cognitive Decline

- Algal DHA supplementation led to a two-fold reduction in the number of errors on a test of memory (PAL)

- Compared to normative data on CANTAB PAL, a 7 year improvement with DHA versus 3.6 year improvement with placebo

- Benefit is roughly equivalent to having the learning and memory skills of someone three years younger on this memory test.

- What is the mechanism? Changes in blood flow or reduction in neuro-inflammation, or both or?

Lower RBC omega 3 levels are associated with poorer visual memory, executive function and abstract thinking.

- **Goal:** To examine the relation of RBC DHA to performance on cognitive tests and to volumetric brain MRI analysis

- **Trial Design:** Cross sectional study to assess the relationship of RBC DHA on subclinical markers of risk for dementia as measured by MRI and neuropsychological tests (*dementia-free Framingham Offspring Cohort participants*), (*Tan et al Neurology 2012*)

  - N= 1,575 (854 women; 721 men) Mean age 67+-9 years

**Measures**

- **Volumetric MRI:** Total cerebral brain volume
- **Neurological tests:** Verbal memory, visuospatial memory, abstract reasoning skills, attention and executive function

- **RBC DHA levels/Omega 3 Index** (DHA+EPA RBC as % total fatty acids)
Results

- **MRI**: comparing persons with RBC DHA + EPA in the lowest quartile (3.9%) versus higher 3 quartiles (Q2-4)
  - Lower quartile of DHA + EPA had significantly lower cerebral brain volume compared with those in higher quartiles
  - This change in volume is equivalent to approx 2 years of structural brain aging
- **Cognitive measures**: RBC DHA + EPA levels showed a continuous positive association with performance in:
  - Visual memory
  - Executive function
  - Abstract thinking

**Conclusion** - Lower RBC omega 3 fatty acid levels were associated with smaller brain volumes and a pattern of cognitive impairment even in persons free of clinical dementia. Suggest confirm in other populations.
Positive Association Between n-3 LCPUFA Supplement Intake and Better Cognitive Functioning (The ADNI cohort study)

GOAL: To evaluate the effects of n-3 LCPUFA supplement intake on rates of brain atrophy and cognitive decline in older adults

TRIAL DESIGN:
- Retrospective cohort study
- Comparing cognitive functioning and brain atrophy in those routinely using LCPUFA supplements versus those who did not.
- 819 subjects recruited from the Alzheimer's Disease Neuroimaging Initiative (ADNI)

RESULTS:
In APOE4(-) group, LCPUFA supplement intake was associated with significantly lower mean ADAS-cog and higher MMSE score along with significantly higher mean hippocampal and cerebral cortex volume, and lower ventricular volume during the study compared to non-users.

Conclusion: Suggests benefits of n-3 PUFA supplementation on brain health and ageing (an association study).

Submitted for publication, Daiello 2011. Reported July 2011 International Conference on Alzheimer's Disease, Deakin University
EPA and DHA improved geriatric depression scores

- **Aim**: determine effect of EPA and DHA on depressive symptoms, QOL and cognition in elderly people with mild cognitive impairment.
- Fifty people aged >65 y in 6-month study with EPA rich, DHA rich or n-6 PUFA, Forty people completed study.
- **Results**: the geriatric depression scores improved in both EPA and DHA groups (p=0.04, 0.01, respectively).
- Verbal fluency improved in DHA group (p=0.04).
- No effect of treatment on QOL.
- **Conclusion**: n-3 PUFA, especially DHA, may reduce depressive symptoms and risk of progression to dementia.

Sinn et al Brit J Nutr 2012
Recent review paper on cognitive enhancement by omega 3 – animal and clinical studies; Luchtman & Song, Neuropharmacol 2013

- 15 page article,
- 1 page on human studies,
- ½ page on observational,
- ½ page on clinical.
- “Mild beneficial effects….in healthy elderly
- “Research that compares EPA with DHA is lacking..
- “Improved systematic approach & control over experimental design to testing of PUFA...
EU research project will provide ‘definitive’ evidence on healthy aging: Bischoff-Ferrari

By Nathan Gray, 00-Feb-2012

DO-HEALTH: Europe starts largest healthy aging study EU partners with Nestle, DSM and Roche Diagnostics

DO-HEALTH will study impact of Vitamin D3, Omega3 and exercise on aging

- 12.8 mio Euro
- > 2100 participants in 5 countries and 8 centers, during 3 years
- Focus on prevention!

A new international study hopes to provide definitive evidence that vitamin D, omega-3, and exercise can reduce the burden of chronic diseases in the elderly.

The European Commission backed DO-HEALTH study (VitaminD3-Omega3-Home Exercise-Healthy Ageing and Longevity Trial) will be Europe’s largest healthy ageing study, and is expected to provide solid evidence for the efficacy and safety of three simple preventive interventions: vitamin D, omega-3 fatty acids and a simple home exercise programme, says the projects principle investigator Professor Heike Bischoff-Ferrari.

Vitamin D expert Bischoff-Ferrari, who is director of the Centre on Aging and Mobility at Zurich University, told Nutritionalists that the new 12.8 million Euro research project “is an attempt to create evidence for three simple strategies to improve health at older age.”

She explained that there is a wealth of information in the scientific literature that suggests vitamin D, omega-3 fatty acids, and exercise can all help to improve health endpoints. However, the evidence for
Key Issues

Alzheimer’s disease is the main form of dementia

Risk factors – some related to diet & lifestyle

Age is a major risk factor for dementia

Avoid head injuries, cardiovascular disease and maintain an active brain

Some preliminary evidence for reducing or slowing dementia with “medical foods”, including the long chain omega 3 FA, especially DHA

Healthy food pattern associated with variety of natural foods

Deakin University
Thank you for listening
The brain is rich in long chain PUFA: fingerprint

The brain is rich in long chain PUFA: fingerprint

Data as percent of total grey matter fatty acids

Deakin University