Omega-3 Fatty Acids and Brain Health

Dr Alex Richardson

Senior Research Fellow, Centre for Evidence-Based Intervention, University of Oxford

Founder Director, Food and Behaviour Research
The Modern, Western-Type Diet

- Modern, ‘junk food’ diets are seriously damaging our physical health – leading to increased rates of:
  - Obesity
  - Type-II Diabetes
  - Heart Disease
  - Cancer
  - Allergies / Immune Disorders

- Diet also affects our brains and behaviour
“A Rotten Way to Feed the Children”

16 Apr 2004 - Times Educational Supplement
By Stephanie Northern

“The physical risks to children from a nutritionally poor diet are now acknowledged, but the damage being done to their behaviour, learning abilities and mood is not.”

• The UK Government has been forced to pump £342 million into school behaviour improvement programmes.

• The WHO predicts a 50 per cent rise in child mental disorders by 2020.

• Dyslexia, hyperactivity, autism and related conditions all appear to be on the increase.

© A.J.Richardson, Food And Behaviour Research 2012
Increasing Costs of Mental Health Disorders

UK (Government’s own figures)

• In 2007: £77 billion
• In 2010: £105 billion

Europe

• In a typical year, 38% of Europeans (≈165 million) will have a fully developed mental / neurological illness.

Witchens et al 2011, The size and burden of mental disorders and other disorders of the brain 2010
Most Common Mental Health Disorders

Europe

- Anxiety disorders 14.0%
- Insomnia 7.0%
- Major depression 6.9%
- Somatoform 6.3%
- Alcohol and drug dependence 5.4%
- ADHD 5% in the young
- Dementia 1–30%, depending on age

Witchens et al 2011, The size and burden of mental disorders and other disorders of the brain 2010

© A.J.Richardson, Food And Behaviour Research 2012
Importance of omega-3 for brain development and function

• Omega-3 were only recognised as essential nutrients in the 1960s

• The long-chain omega-3 (EPA and DHA) are critical for the normal structure and function of the brain and nervous system

‘Dietary shifts’ over the last century (↓ seafood intakes, ↑ vegetable oils) have reduced tissue levels of these omega-3
Dietary Sources of Omega-6

omega-6

EFA

LA (Linoleic) 18:2

GLA 18:3

DGLA 20:3 *

HUFA

AA (Arachidonic) 20:4 *

Adrenic 22:4

DPA(n-6) 22:5

Vegetable oils, nuts, seeds, grains

Evening primrose oil

Meat, eggs, dairy products (milk cheese, butter, yogurt etc)
Dietary Sources of Omega-3

**omega-3**

- ALA (α-linolenic) 18:3
- EPA 20:5 *
- DPA(n-3) 22:5
- DHA 22:6
- 18:4
- 20:4

Green leafy vegetables, seaweed, & some nut & seed oils (flax, walnut, chia, canola/rapeseed)

Fish and seafood
Human development is about the growth of the BRAIN, not the body – and Nutrition is simply critical
The human brain is 60% FAT and it matters what kind.

Some Fats are Essential
- Omega-3 and Omega-6 Polyunsaturates
Synthesis of Highly Unsaturated Fatty Acids (HUFA) from ‘Essential’ Fatty Acids (EFA)

<table>
<thead>
<tr>
<th>'EFA'</th>
<th>omega-6</th>
<th>omega-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA (Linoleic)</td>
<td>18:2</td>
<td>ALA (A-linolenic) 18:3</td>
</tr>
<tr>
<td>GLA</td>
<td>18:3</td>
<td>18:4</td>
</tr>
<tr>
<td>DGLA</td>
<td>20:3 *</td>
<td>EPA</td>
</tr>
<tr>
<td>AA (Arachidonic)</td>
<td>20:4 *</td>
<td>DPA(n-3)</td>
</tr>
<tr>
<td>Adrenic</td>
<td>22:4</td>
<td>DHA</td>
</tr>
<tr>
<td>DPA(n-6)</td>
<td>22:5</td>
<td></td>
</tr>
</tbody>
</table>

PUFA (Polyunsaturated Fatty Acids)

© A.J.Richardson, Food And Behaviour Research 2012
Conversion of HUFA to Eicosanoids

- **Endocannabinoids** (2-AG, Anandamide)
- **Resolvins**
- **Docosanoids (neuroprotectins)**

**n-6**
- Dietary LA → LA → 15-LOX → 9-HODE, 13-HODE
- Dietary GLA → GLA → Δ⁵-Desaturase → 18:4n-3 → 1-series PGs, TXs
- Dietary AA → Membrane Phospholipids

**n-3**
- Dietary α-LNA → α-LNA → Δ⁵-Desaturase → 20:4n-3
- Dietary EPA
- Dietary DHA

**Eicosanoids**
- **COXs**
  - PGG₂ → PGH₂ → PGI₂
  - 15d-PGJ₂ → PGE₂ → PGF₂α
  - TXA₂

- **5-LOX**
  - 5-HPETE
  - 5-HETE
  - LTA₄
  - LTA₅
  - 5-HEPE
  - 12-HEPE
  - 15-HEPE

- **12-LOX**
  - 12-HPETE
  - 12-HETE

- **15-LOX**
  - 15-HPETE
  - 15-HETE

© A.J. Richardson, Food And Behaviour Research 2012
What are omega-3 essential for?

1. The structure of all cell membranes
   - Omega-3 (and omega-6) LC-PUFA increase membrane fluidity, essential for optimal cell signalling
   - 6-10% of the dry mass of the brain should be DHA
   - DHA is particularly concentrated in nerve terminals, where chemical signals between cells are exchanged
   - Concentrations of dopamine, serotonin, noradrenalin, acetylcholine etc are influenced by omega-3 status
Omega-3 and Vision

Long-chain Omega-3 are essential to the visual system

- 30-50% of the retina should be made of the omega-3 DHA
- DHA deficiency can reduce retinal signalling by more than a thousand-fold
- Omega-3 deficiency is associated with problems with visual, spatial and attentional processing, including age-related vision loss (poor night vision, and macular degeneration).
What are omega-3 HUFA essential for?

1. The structure of all cell membranes
   - Omega-3 (and omega-6) increase membrane fluidity, essential for optimal cell signalling

2. Brain development
   - Fatty acids make up around 20% of dry brain mass, and affect brain growth and connectivity
   - Supplementing infant formula with HUFA (found naturally in breastmilk) can improve visual and cognitive development
Growth of Brain Cells Enhanced by DHA

Calderon and Kim, J. Neurochem. 2004
Omega-3 deficiency impairs synapse development

<table>
<thead>
<tr>
<th></th>
<th>Adequate</th>
<th>Deficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA</td>
<td>6.6 ± 0.7%</td>
<td>0.5 ± 0.1%</td>
</tr>
<tr>
<td>DPAn-6</td>
<td>0.4 ± 0.1%</td>
<td>4.7 ± 0.1%</td>
</tr>
</tbody>
</table>

Hippocampal Fatty Acids

Synapses in Hippocampal Neurons


Embryo neurons day 18

© J Hibbeln, NIH, 2012
‘NUTRITIONAL PROGRAMMING’
Adverse Mental Health Effects from ‘Western-Type’ Dietary Fat Intake in Early Life


- **Trevizol et al. (2011)** Comparative study between n-6, trans and n-3 fatty acids on repeated amphetamine exposure: a possible factor for the development of mania. *Pharmacol Biochem Behav*. 97(3) 560-5.


© A.J. Richardson, Food And Behaviour Research 2012
What are omega-3 HUFA essential for?

1. The structure of all cell membranes
   - Omega-3 (and omega-6) increase membrane fluidity, essential for optimal cell signalling

2. Brain development
   - Fatty acids make up around 20% of dry brain mass, and affect brain growth and connectivity
   - Supplementing infant formula with HUFA (found naturally in breastmilk) can improve visual and cognitive development

3. Maintenance of optimal brain function throughout life
   - Cell signalling depends on membrane fluidity
   - Omega-3 and omega-6 fatty acids and their derivatives have very powerful effects on most brain signalling systems
   - The substances we make from them can profoundly affect hormone balance, blood flow and immune system function

© A.J. Richardson, Food And Behaviour Research 2012
Omega 6 and Omega-3 ‘functional fats’
– a matter of balance

The omega-6 AA
(from meat, eggs and dairy products – or converted from LA in vegetable oils)
gives rise to substances that
• promote inflammation
• promote blood clotting
• narrow blood vessels

The omega-3 EPA
(from fish and seafood – or converted from ALA in green leafy vegetables, flax seed etc)
gives rise to substances that
• reduce inflammation
• reduce blood clotting
• relax blood vessels

A few simple dietary changes can make a big difference
• Eat more: fish and seafood, green vegetables, nuts, seeds
• Eat less: meat, dairy products, refined vegetable oils
Dietary need for Omega-3 (EPA/DHA)*

*Available evidence does not show similar health benefits from shorter-chain omega-3 (ALA), derived from plant sources

Recommendations from international scientific & health organisations

- General population - cardiovascular health:

- Depression or other mental health conditions:
  - ≥ 1000mg (1g) / day EPA+DHA ([APA Freeman et al 2006, Hibbeln & Davis 2009](#))

- In the UK, US, Australia and Canada, most people consume less than 150mg/day
If dietary intake of omega-3 is increased, will it help?

Evidence from Randomised Controlled Trials
Dysfunctions of Body and Mind that long-chain Omega-3 (EPA and DHA) may help to prevent or ameliorate

• Cardiovascular Disease
  – Heart Disease and Stroke

• Inflammatory / Auto-immune Disorders
  – e.g. Rheumatoid Arthritis

• Visual Problems
  – ‘Retinopathies’ of Prematurity, Diabetes, Old Age

• Disorders of Behaviour, Learning and Mood
  – ADHD and related childhood developmental disorders
  – Depression, Schizophrenia and other mental health problems
  – Age-related cognitive decline and dementia?
Omega-3 from fish oils are effective in reducing ADHD symptoms.
THE OXFORD-DURHAM STUDY:
A randomised controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder.


117 underachieving children aged 5-12 years from mainstream schools

- All showed specific difficulties in motor coordination (DSM-IV DCD)
- 40% were behind expected achievement in reading and spelling
- Over 30% scored in the clinical range for ADHD-type symptoms (>2SD above population means)
Behaviour Ratings

Reduction in ADHD-related Symptoms

- DSM Combined-type
- DSM Hyperactivity
- DSM Inattention
- Conners Global Index
- CG Emotional Lability
- CG Restless-Impulsive
- Conners Index
- Social Problems
- Perfectionism
- Anxiety
- Hyperactivity
- Cognitive Problems
- Opposition

Treatment Effect Size
(Mean change 0-3m / Pooled Baseline SD)

Placebo (N=52)
Active (N=50)

© A.J.Richardson, Food And Behaviour Research 2012
Reading and Spelling


**Active treatment**

- Compared with expected progress for normal children, gains were > 3 x normal rate for reading, > 2 x for spelling

**Placebo**

- Gains were 1 x normal rate for reading, < 0.5 x for spelling

**Group Differences**

- Reading  p < 0.004
- Spelling  p < 0.001
The DHA (Docosahexaenoic Acid) Oxford Learning And Behaviour (DOLAB) Study
RCTs of Omega-3 for Mood Disorders

In Adults

• Five recent ‘meta-analyses’ show:
  – Significant benefits for depression (+ bipolar disorder)
    • American Psychiatric Association recommends >1g/day EPA+DHA as an add-on treatment for mood disorders
      (Freeman et al, J. Clin Psychiat. 2006)
  – Mixed results from studies including more varied populations and treatments (Appleton et al 2006, Rogers et al 2008)

In Children

• One pilot RCT to date, showing significant benefits for children with depression (Nemets et al, Am.J.Psychiat. 2006)
Omega-3 for Depression - EPA vs DHA?


<table>
<thead>
<tr>
<th>Study</th>
<th>Standardized Mean Difference (95% CI)</th>
<th>% EPA</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peet and Horrobin, 2002</td>
<td></td>
<td>100</td>
<td>9.40</td>
</tr>
<tr>
<td>Nemets et al, 2002</td>
<td></td>
<td>100</td>
<td>5.60</td>
</tr>
<tr>
<td>Frangou et al, 2006</td>
<td></td>
<td>100</td>
<td>14.20</td>
</tr>
<tr>
<td>Peet and Horrobin, 2002</td>
<td></td>
<td>100</td>
<td>9.70</td>
</tr>
<tr>
<td>Peet and Horrobin, 2002</td>
<td></td>
<td>100</td>
<td>9.40</td>
</tr>
<tr>
<td>Mischoulon et al, 2009</td>
<td></td>
<td>100</td>
<td>8.30</td>
</tr>
<tr>
<td>Frangou et al, 2006</td>
<td></td>
<td>100</td>
<td>13.90</td>
</tr>
<tr>
<td>Su et al, 2003</td>
<td></td>
<td>66.67</td>
<td>6.80</td>
</tr>
<tr>
<td>Nemets et al, 2006</td>
<td></td>
<td>66.67</td>
<td>5.60</td>
</tr>
<tr>
<td>Su et al, 2008</td>
<td></td>
<td>64.71</td>
<td>9.20</td>
</tr>
<tr>
<td>da Silva et al, 2008</td>
<td></td>
<td>60</td>
<td>3.60</td>
</tr>
<tr>
<td>da Silva et al, 2008</td>
<td></td>
<td>60</td>
<td>4.40</td>
</tr>
<tr>
<td><strong>Overall EPA ≥ 60%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freeman et al, 2008</td>
<td></td>
<td>57.89</td>
<td>9.50</td>
</tr>
<tr>
<td>Carney et al, 2009</td>
<td></td>
<td>55.36</td>
<td>20.70</td>
</tr>
<tr>
<td>Rogers et al, 2008</td>
<td></td>
<td>42.57</td>
<td>35.50</td>
</tr>
<tr>
<td>Grenyer et al, 2007</td>
<td></td>
<td>21.43</td>
<td>11.50</td>
</tr>
<tr>
<td>Rees et al, 2008</td>
<td></td>
<td>20.18</td>
<td>4.00</td>
</tr>
<tr>
<td>Silvers et al, 2005</td>
<td></td>
<td>20</td>
<td>12.70</td>
</tr>
<tr>
<td>Marangell et al, 2003</td>
<td></td>
<td>0</td>
<td>6.10</td>
</tr>
<tr>
<td><strong>Overall EPA &lt; 60%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© A.J. Richardson, Food And Behaviour Research 2012
Prevention of Psychosis (Schizophrenia)

Amminger et al (2010) Archives of General Psychiatry 67(2) 146-54

- 81 young people at ultra-high risk for psychosis
  - Age 13-25 yrs
- 12 weeks treatment with 1.2g long-chain omega-3
  - 700mg EPA, 500mg DHA from fish oils
- Assessments over 12 months
  - Baseline, 1, 2, 3, 4, 8, 12 weeks, then 6 & 12 months
- Primary outcome:
  - Transition to psychosis
- Secondary outcomes:
  - Measures of symptoms & functioning
  - Blood fatty acids

© A.J.Richardson, Food And Behaviour Research 2012
RESULTS at 12 month follow-up

Primary outcome: transition to psychosis (p=0.007, NNT=4).

- Omega-3: 2/41 (4.9%)
- Placebo: 11/40 (27.5%)

© A.J. Richardson, Food And Behaviour Research 2012
Other psychological / psychiatric conditions?

- Autistic Spectrum Disorders
- Anxiety Disorders
- Borderline Personality Disorder
- Self-harm
- Stress / Hostility / Aggression
- Age-related Cognitive Decline
- Alzheimer’s Disease (early stage)

In each case, pilot RCTs have provided some preliminary evidence of possible benefits, but more research is needed.
SUMMARY

• Long-chain Omega-3 (EPA and DHA) are essential for brain development and function

• In most developed countries, median intakes are below recommendations for cardiovascular / general health

• Low blood concentrations of EPA/DHA are associated with difficulties affecting mood, behaviour and learning

• RCT evidence shows that dietary supplementation with EPA/DHA can be of benefit for:
  – Cardiovascular and immune system health
  – ADHD, depression / bipolar disorder
  – Possible prevention of schizophrenia and other psychological disorders

© A.J. Richardson, Food And Behaviour Research 2012
Further Information
For details of this and related research see
Food And Behaviour Research
www.fabresearch.org

© A.J. Richardson, Food And Behaviour Research 2012
Omega-3 deficiency in Early Life and Mental Disorders: Evidence for mechanisms

Omega-3 deficiency during pregnancy leads to behavioural deficits in the offspring consistent with anxiety and depression. Mechanisms now identified include:

• Permanent impairment of endocannabinoid-mediated neuronal plasticity in hippocampal networks
  

• Permanent disruption of BDNF, neuropeptide Y-1 & glucocorticoid receptors, and insulin signalling in frontal cortex, hypothalamus and hippocampus
  
Blood levels of omega-3 HUFAs and health

17% US MILITARY ACTIVE DUTY

20% TAKE URGENT REMEDIAL ACTION

30% TAKE REMEDIAL ACTION

40% REMEDIAL ACTION BENIFICIAL

50% HEALTHY OMEGA-3 LEVEL

60% ADJUST FOR OPTIMAL HEALTH

70% OPTIMAL HEALTH
Deliberate Self-Harm

Copyright Joe Hibbeln 2012

• Subjects n = 49
• Recruited from a Dublin emergency room
• 12 week, double-blind, placebo-controlled trial
• 2.1 g/d, (1.2 g/d EPA, 0.9 g/d DHA)
• (EPAX 5500, Pronova Biocare, Norway)

Results
• 50% reduction in depression (Beck)
• 45% reduction in suicidal thinking (OAS)
• 33% reduction in perception of stress (PSS)
• 30% improvement in “happiness” (DHUS)
• (perception of daily events as uplifting)
Age-Related Cognitive Decline and Dementia

• Epidemiological evidence
  – Higher intakes of omega-3 from seafood (EPA + DHA) are protective against dementia, and associated with higher intelligence and mental agility in older adults (Whalley et al 2006)

• Biochemical and MRI studies
  – Low blood omega-3 is associated with impaired attention, memory and other aspects of cognitive function in adults – and with reduced brain volume in older adults (Tan et al 2012)

• Controlled treatment trials
  – Memory / Mild Cognitive Impairment in older adults: significant benefits in only one of 3 recent RCTs (Yurko-Mauro et al 2010)
  – Prevention of ARCD: 3 RCTs show no evidence of benefit (Sydenham et al 2012) although study design is a major problem (Dangour 2012)
Reading - Change Scores by Treatment Group

Word Reading (age-standardized)

<table>
<thead>
<tr>
<th>Group</th>
<th>Active Score</th>
<th>Placebo Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Sample (n=362)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=20% Readers (n=224)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=10% Readers (n=105)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistical Significance:
- p = .28
- p = .04
- p < .01
Parent-Rated Behaviour – Sub-Scales

Change Scores for CPRS-L (Sub-Scales)

Whole Sample (n=362)

- Oppositional
- Cognitive Problems
- Hyperactivity
- Anxiety
- Perfectionism
- Social Problems
- Psychosomatic

Mean Change Score (Pre-Post Intervention, Mean ±1 SE)

-7 -6 -5 -4 -3 -2 -1 0

- p=.01
- p=.06
- p=.02
- p=.07
- p=.68
- p=.16
- p=.17

Active  Placebo
Parent-Rated Behaviour – Global Scales

Change Scores for CPRS-L (Global-Scales)
Whole Sample (n=362)

- ADHD Index
- Restless Impulsive
- Emotional Liability
- Global Total
- DSM-IV Inattention
- DSM-IV Hyperactive
- DSM-IV Total ADHD

Mean Change Score (Pre-/Post-Intervention) (Means ±1 SE)

Significance Levels:
- p=.04
- p<.01
- p<.01
- p<.01
- p=.09
- p=.02
- p=.03

Legend:
- Active
- Placebo