

Healthy Fats for Brain Health

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Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

Organization	Support	Role
Nordic Naturals	Donated drug and placebo for clinical trial	Clinical investigator
heckel medizintechnik GmbH	Donated Whole Body Hyperthermia device for clinical trial	Clinical investigator
MGH Clinical Trials Network and Institute (CTNI)	Salary support through CTNI from multiple pharmaceutical companies and NIMH	Clinical Rater and Director of Training

Introduction

- Nutrition is important in mental health
- Fats are essential for brain structure, function, and signaling
- Diet impacts cognition and mood

Fats



Butter



Oil



Nuts



Avacados



Meats & Fishes

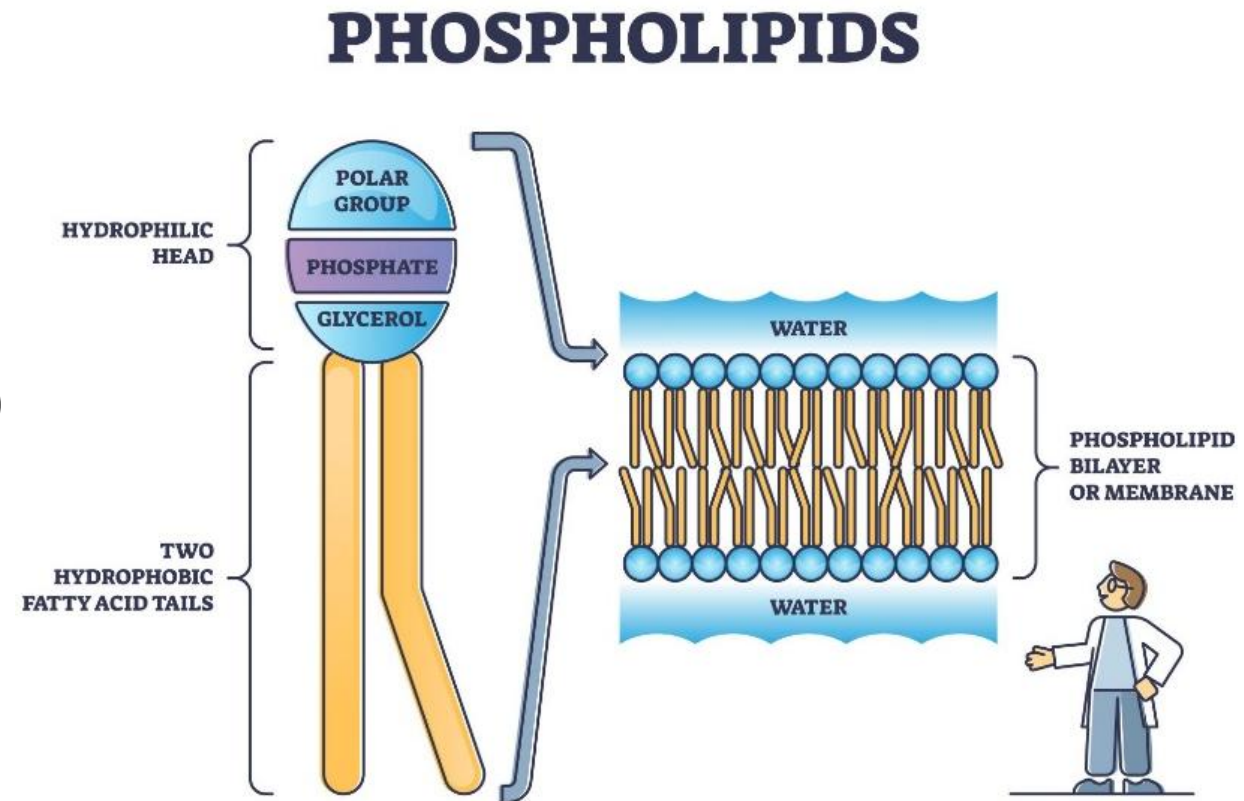


Chocolates

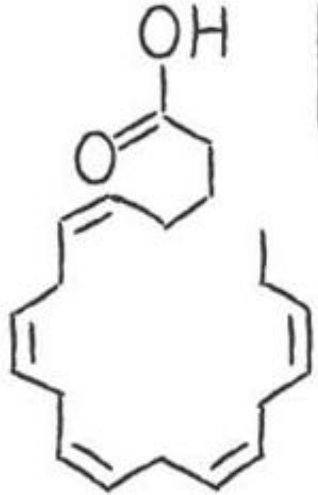


Brain Lipid Composition

- ~60% of the dry brain is fat
- Key structural components
 - Phospholipids
 - Cholesterol
 - Polyunsaturated fatty acids (PUFA)
 - esp. omega-3 and omega-6
- Important for
 - Myelin formation
 - Membrane fluidity
 - Neurotransmitter function

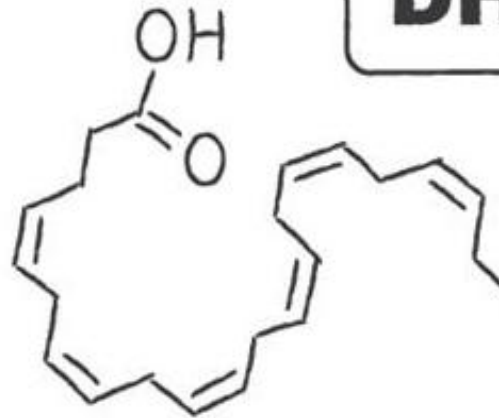


Omega-3 Fatty Acids: DHA and EPA



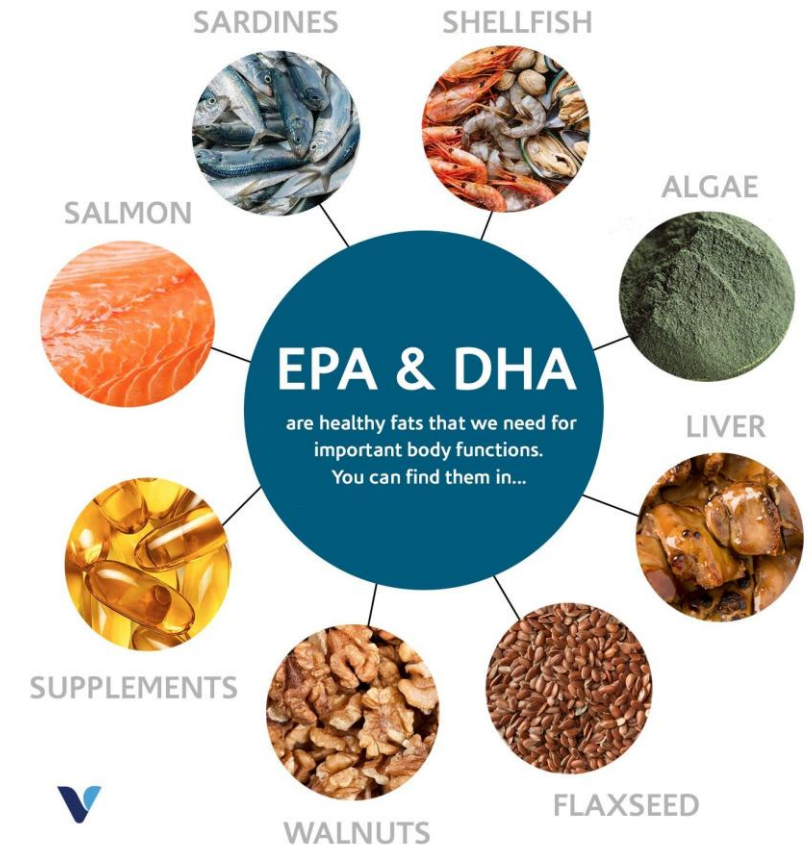
EPA

Eicosapentaenoic Acid (EPA) (20:5, n-3)



DHA

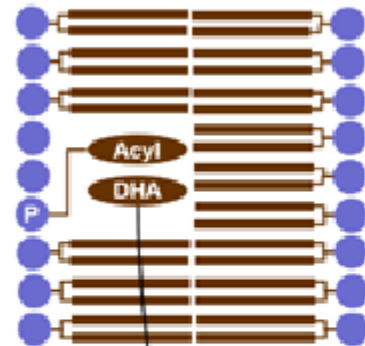
Docosahexaenoic Acid (DHA) (22:6, n-3)



DHA

Neuron growth
Synapse development
Membrane fluidity

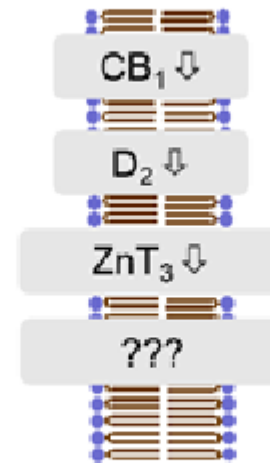
Structural element
DHA as component of neural
membrane phospholipids



PLA2

DHA

Neurotransmitter
DHA as regulator
of release and activity

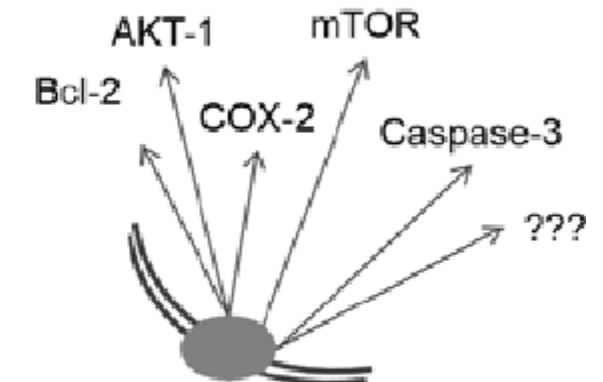


17S-
HpDHA

16S, 17S-
DHA-Epoxid

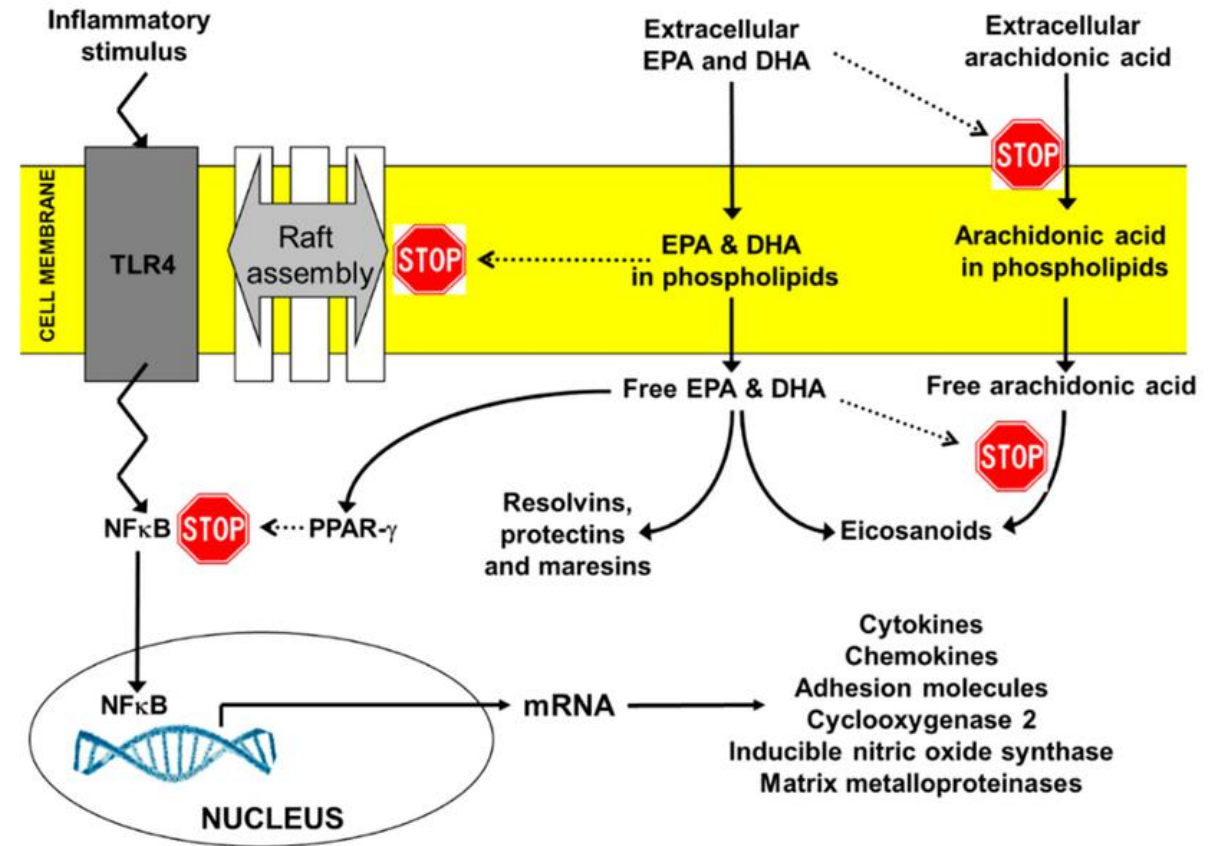
NPD1

Gene expression
DHA as regulator
of gene expression



EPA

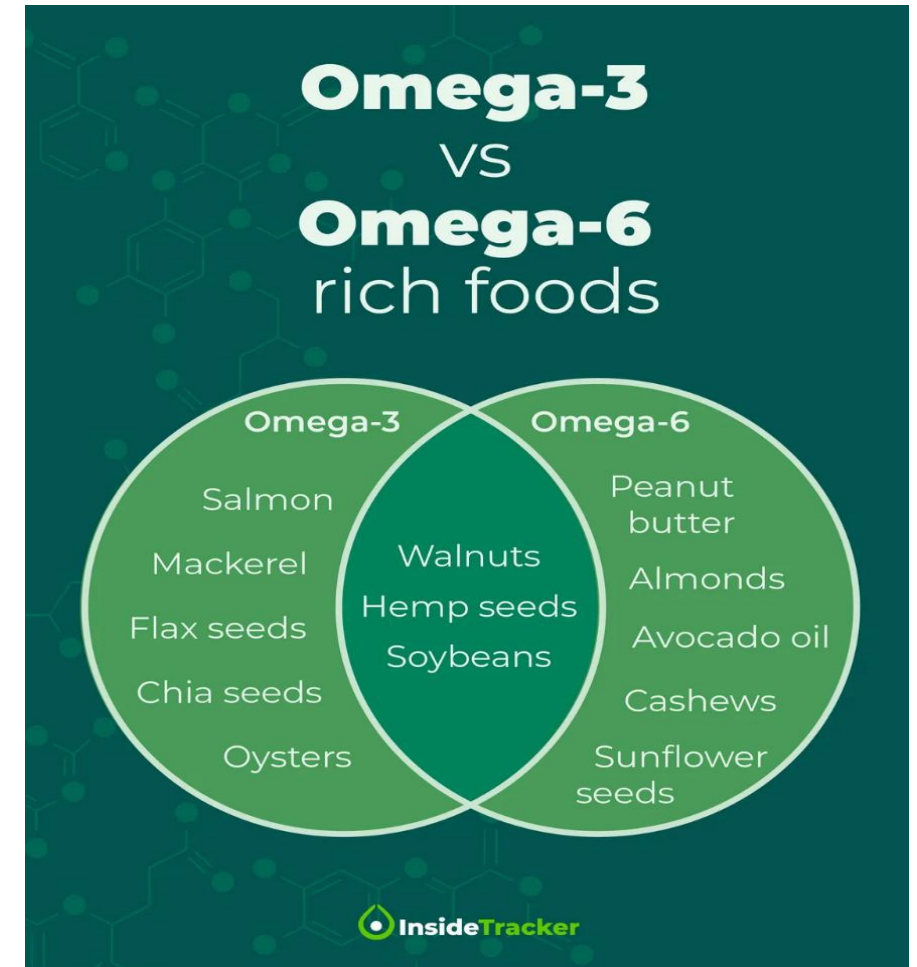
- Less structural than DHA
- Anti-inflammatory
- Modulates mood, inflammation pathways
- Evidence
 - Reduced EPA in depression, bipolar disorder, schizophrenia
 - Meta-analyses: modest benefit of EPA > DHA in major depressive disorder



Sublette et al., 2011; Mocking et al., 2016

Omega-6 Fatty Acids and the Omega-6/Omega-3 Ratio

- Western diet rich in linoleic acid (LA)
 - Abundant in processed foods, seed oils
- Overabundance → pro-inflammatory eicosanoids
- Ideal ratio between 1:1 and 4:1
 - But Western diets often have $\geq 10:1$
- Imbalance → neuroinflammation and mood dysregulation



Saturated and Trans Fats

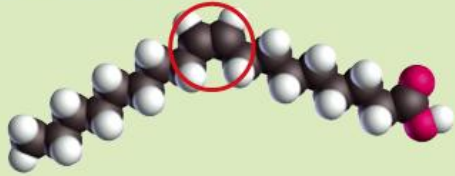
Types of Fatty Acids	Examples of Sources	Health Impacts and Intake Recommendations
Saturated  • No double bond • Straight structure • Solid at room temperature	 Beef  Butter  Coconut oil	• Increase risk of heart disease • Less than 20g of saturated fats per day (for a 2000 kcal diet) • Some benefit <i>in moderation</i>
Trans Partially hydrogenated  • One or more double bonds in trans configuration • Straight structure • Semi-solid/Solid at room temperature	 Margarine  Cream soup with puff pastry  Chicken pie	• Increase risk of heart disease • Less than 2.2g of trans fats per day (for a 2000 kcal diet)

Associated with cognitive decline and systemic inflammation

Recommendation: minimize intake

Mono and Polyunsaturated Fats

Monounsaturated



- One double bond in cis configuration
- Bent structure
- Liquid at room temperature



Olive oil



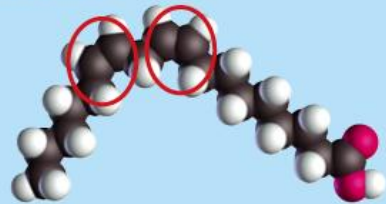
Canola oil



Peanut oil

- May reduce risk of heart disease
- Moderate intake of monounsaturated fats
- Improved cognition
- Reduced risk of depression, Alzheimer's

Polyunsaturated



- Multiple double bonds in cis configuration
- Even more "bent" in structure
- Liquid at room temperature



Soybean oil



Corn oil



Fatty fish

- May reduce risk of heart disease
- Moderate intake of polyunsaturated fats
- Improved cognition
- Reduced risk of depression, Alzheimer's

Mechanisms: enhanced cerebral perfusion, anti-inflammatory effects

Clinical Applications

- **Dietary patterns**

- Mediterranean diet: best evidence for cognitive and mental health benefits
- MIND diet: Mediterranean-DASH Intervention for Neurodegenerative Delay
 - Green, leafy vegetables; non-starchy vegetables; berries; nuts; olive oil; whole grains; fatty fish; beans; poultry
 - Tailored to reduce Alzheimer's risk

- **Supplementation**

- Omega-3s (esp. EPA-predominant) may be useful adjuncts in MDD and bipolar depression
- Dose considerations: 1–2g EPA/day with low DHA for depression

- **Caveats**

- Not all patients respond
- Interaction with psychotropic meds is minimal, but should monitor

Efficacy of Omega-3 Supplements

- **Unipolar Major Depression**
- Dozens of RCTs, mostly adjunctive omega-3
 - EPA and EPA+DHA combinations used most often; 1-2 g/day
 - Up to 4 g/day for depression with high inflammation (Mischoulon et al, 2022)
 - Recommended $\geq 60\%$ EPA in combinations (Sublette et al, 2011)
- Limited evidence for DHA (Marangell et al, 2003; Mischoulon et al, 2008; Lewis et al, 2011; Mischoulon et al, 2015)
 - Few studies
 - Unclear optimal doses
 - Limitations of study design
 - Maybe preventive effect against suicide?

Efficacy of Omega-3 Supplements

- **Postpartum depression?** (Freeman et al, 2006; Marangell et al, 2004)
 - Pregnancy depletes omega-3 in the mother
 - Necessary for developing brain (neural development, allergy prevention)
 - FDA supports fatty fish consumption in pregnancy
 - Safe upper limit of doses is unknown
- **Bipolar disorder?** (Stoll et al, 1999; Keck et al, 2006)
 - Best for depressed phase rather than mania (Sarris et al, 2012)
 - Omega-3 may trigger cycling to mania (doses of 6-10 g/day sometimes used)
 - Need caution in bipolar disorder

Safety

- Common side effects include stomach upset, fishy taste
 - Less so with current, highly purified preparations
- Concerns about bleeding at doses >3 g/day probably exaggerated
- Concerns about atrial fibrillation with higher doses are unclear
- Generally very safe but caution required with certain populations
 - Pregnancy, bipolar disorder, bleeding disorders, preoperatively

Omega-3s in Action: Bill

- 40-year-old male, h/o recurrent depression
- Prone to side effects from antidepressants
- Recently started on fluoxetine 20mg/day
- Increased dose to 40mg with partial response
- Attempts to increase further result in sexual dysfunction
- Remains at 40mg but still symptomatic
- Reluctant to add another antidepressant
- Interested in omega-3 since it is natural



Bill (cont'd)

- We add an EPA/DHA mix at 1000 mg/day
- Increase dose to 2000 mg/day after 4 weeks
- After 4 more weeks, Bill reports he is feeling much better, with no additional side effects



Summary & Recommendations

- The brain is fat-rich; fat is important; the type of fat matters
- Omega-3s (especially EPA) support mood and cognitive health
- A balanced, anti-inflammatory fat profile is neuroprotective
- Encourage whole-food sources of healthy fats
- Shift omega-6/omega-3 ratio toward omega-3
- Diets can be challenging to follow for indefinite periods
- Consider omega-3 supplementation in selected psychiatric patients
- Be cautious with saturated/trans fats

Questions?

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