Note on CogniActiv

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The cognitive ability of humans is arguably the most advanced in the entire animal kingdom. Such advancement is believed to be conferred by an expanded cerebral cortex and a highly developed prefrontal cortex, both of which are brain regions important for cognition. There are many different domains to the clinical construct of cognition. These include attention, memory (working and long-term), perception, language, problem solving, comprehension, reasoning, computation, reading and speech. Cognition changes throughout the lifespan matching the development, maturation and aging of the brain. The brain is a lipid-rich organ that consumes 20% of the body's energy, but it only comprises 2% of the body's mass. Over half of the brain's dry weight is comprised of lipids, and it is especially enriched in long-chain omega-3 (*n*-3) polyunsaturated fatty acids (PUFAs), suggesting a key role for these molecules in the optimal development, maturation and aging of neural structures and networks. A substantial amount of literature exists that highlights the crucial role of nutrition in brain development, and thus on brain function and mental performance in humans. Ultimately, the proper functioning of the brain has significant dependence upon maintaining its optimal lipid composition.

The two main families of PUFAs are omega 6 (linoleic acid) and omega 3 (alpha-linolenic acid). The metabolic product of linoleic acid is the arachidonic acid (AA), and those of the alpha-linolenic acid are the eicosapentaenoic (EPA) and the docosahexaenoic (DHA) acids. These PUFAs might be utilized as mediators of immune and inflammatory responses and as energy source in several physiological systems and membrane structures. These acids are essential for the central nervous system to work well, since about 50% of the brain weight consists of lipids, out of which 20% are PUFAs.

Docosahexaenoic acid (DHA) is the predominant omega-3 (*n*-3) polyunsaturated fatty acid (PUFA) found in the brain and can affect neurological function by modulating signal transduction pathways, neurotransmission, neurogenesis, myelination, membrane receptor function, synaptic plasticity, neuroinflammation, membrane integrity and membrane organization. DHA is rapidly accumulated in the brain during gestation and early infancy, and the availability of DHA via transfer from maternal stores impacts the degree of DHA incorporation into neural tissues.

It is widely recognized that a diet deficient in omega 3 might influences neurotransmission, namely the dopaminergic and the serotonergic systems. As a result, the amount of dopamine can be reduced. Conversely, supplementation with fish oil increases the level of dopamine and reduces monoamine oxidase B activities. Therefore, as in the treatment with medication, the increase in the ingestion of omega 3 might enhance the central activity of dopamine in the pre-frontal cortex over time, thus reducing aggressiveness and impulsiveness.

The consumption of DHA leads to many positive physiological and behavioral effects, including those on cognition. Advanced cognitive function is uniquely human, and the optimal development and aging of cognitive abilities has profound impacts on quality of life, productivity, and advancement of society in general. However, the modern diet typically lacks appreciable amounts of DHA. Therefore, in modern populations, maintaining optimal levels of DHA in the brain throughout the lifespan likely requires obtaining preformed DHA via dietary or supplemental sources.

Quantitatively, docosahexaenoic acid (DHA; 22:6*n*-3) is the most significant *n*-3 PUFA in the brain as both eicosapentaenoic acid (EPA; 20:5*n*-3) and α-linolenic acid (ALA; 18:3*n*-3) are present in only very small quantities. DHA makes up over 90% of the *n*-3 PUFAs in the brain and 10%–20% of its total lipids. DHA is especially concentrated in the gray matter. It is stored primarily in phosphatidylethanolamine (PE) and phosphatidylserine (PS) membrane phospholipids, with smaller amounts also found in phosphatidylcholine, where it plays an important role in the biosynthesis of PS (DHA-PS) in the brain. DHA is enriched in membranes structures found at synaptic terminals, mitochondria and endoplasmic reticulum, and it can ultimately affect cellular characteristics and physiological processes including membrane fluidity, lipid raft function, neurotransmitter release, transmembrane receptor function, gene expression, signal transduction, myelination, neuroinflammation, and neuronal differentiation and growth.

The brain's frontal lobes are particularly responsive to the supply of DHA during development. Decades of work have clearly established the responsibilities of the frontal lobes for executive and higher-order cognitive activities including sustained attention, planning and problem solving , and the prefrontal lobe in particular for social, emotional and behavioral development Therefore, maintaining optimal lipid composition in these brain regions, and specifically DHA levels, is not only important during the development and maturation of the brain from gestation through childhood and adolescence but such maintenance is also critical for successful aging of the adult brain

DHA synthesized *de novo* originates from ALA via a series of desaturations and elongations primarily within the endoplasmic reticulum (ER), with the exception of the last step, a β-oxidation from tetracosahexaenoic acid (24:6*n*-3) that occurs in peroxisomes ALA is considered an essential nutrient because humans lack the *n*-3 desaturase enzyme required for its production. However, it could be argued that DHA is also an essential nutrient due to inefficiencies of the 5-desaturase and 6-desaturase enzymes (FADS1/2) needed for its biosynthesis, and the competition for these enzymes by the omega-6 (*n*-6) PUFA linoleic acid (LA; 18:2*n*-6). LA is typically consumed in high amounts in modern diets, which exacerbates the increase of *n*-6 PUFAs, as well as the decrease of *n*-3 PUFAs, that are incorporated in peripheral and neural tissues Therefore, many researchers conclude that preformed DHA consumption is required for reaching and maintaining ideal brain DHA concentrations and related neurological functions

DHA is acquired during development through gestational placental transfer and from mother's milk during infancy. The levels of DHA in mother's milk can be as high as 1.4% of total fatty acids with a worldwide average of 0.32% of total fatty acids, depending on the mother's diet and number of pregnancies *De novo* DHA synthesis can occur in the liver, however the DHA precursor ALA does not increase plasma DHA in humans (<0.1% conversion efficiency in humans; In fact, neither ALA nor EPA is an effective dietary source of DHA due to the minimal *in vivo* production of DHA from these precursors in humans, indicating that preformed DHA is most effective in maintaining sufficient tissue

stores .On the other hand, DHA supplementation adds to the peripheral tissue pool of EPA, likely due to retroconversion "Attention Deficit / Hyperactivity Disorder", abbreviated as ADHD or ADD, learning disabilities, dyslexia are some of the most common childhood disorders. These disorders can continue through adolescence and adulthood. Common symptoms comprise difficulty staying focused and paying attention, difficulty controlling behavior, and hyperactivity (over-activity), Attention deficit/hyperactivity disorder (ADHD) is a development alteration characterized by impulsiveness, excess of activity and limited capacity to keep attention. Its prevalence all over the world is between 6.5% and 11% among children aged 5 to 15 years. The neurobiological alterations include dysfunction in the dopaminergic transmission in the striatal structures and frontal lobes. and a lower brain volume. These affected brain areas correspond to attention and executive functions (working memory, motor control and inhibition).

Inattention, hyperactivity, and impulsivity are the key behaviors of ADHD. It is normal for all children to be inattentive, hyperactive, or impulsive sometimes, but for children with ADHD, these behaviors are more severe and occur more often. To be diagnosed with the disorder, a child must have symptoms for 6 or more months and to a degree that is greater than other children of the same age.

Studies show that the number of children being diagnosed with ADHD is increasing.

Recognizing ADHD symptoms and seeking help early will lead to better outcomes for both affected children and their families.

Adults may also have ADHD symptoms. This particularly possible when the ADHD symptoms began in childhood and have continued throughout adulthood.
Although there is no cure found so far, treatments that relieve many of the disorder's symptoms focus on reducing the symptoms of ADHD and improving functioning and include medication, various types of psychotherapy, education or training, or a combination of treatments.
However, need for Research is recognized for developing more effective treatments and interventions, and using new tools such as brain imaging, to better understand ADHD and to find more effective ways to treat and prevent it.

Childhood is a critical and vulnerable period in which the supplementation with PUFAS is fundamental for the good working of the brain. PUFAs, especially DHA and AA, accumulate rapidly in the gray matter of the brain in this period, and its deficiency may cause deficits in memory, learning, mood and the sensorial system that can be irreversible. Therefore, a diet rich in DHA might play a crucial role in the cognitive development and neural disorders of children.

Mechanisms of DHA Actions during Development
As already outlined, DHA is accumulated in the brain tissue mainly during the second half of pregnancy and during the first two years of life Currently the consumption of one to two portions of fish per week, including oily fish, which is a rich source of DHA, is recommended. The challenging question is: What are DHA's actions in the developing brain that lead to gains in cognitive function? This question is far from being answered, but several pathways can be identified, many of which overlap with those occurring during adulthood and aging (described in a subsequent section).

DHA, as the most abundant *n*-3 PUFA in the brain and retina, contributes to the structure of brain cell membranes. DHA is also implicated in neurogenesis, neurotransmission, and cell survival within the CNS DHA contributes to cell membrane fluidity and to signal transduction within the CNS by activating cell membrane receptors DHA also alters gene expression in mammalian brain tissue that influences neurite outgrowth and learning and memory The process of neurite outgrowth in hippocampal neurons is enhanced by DHA, which may in turn promote learning Growth of neurites requires the accumulation of lipids in new membranes, and DHA helps to organize lipid raft domains in the membrane by pushing cholesterol into these structures important for neurite extension, myelination, and membrane-mediated signaling Also important for neurite outgrowth, DHA enhances protein kinase B (PKB; also known as Akt) signaling and in turn the mTOR (mechanistic target of rapamycin) complex, which promotes neuronal growth DHA improves learning and memory by facilitating the formation of pre- and postsynaptic proteins that enable synaptic transmission and long-term potentiation (LTP) Under oxidative stress, DHA can promote repair and growth of neurons by activating peroxisome proliferator-activated receptor gamma (PPAR) and through its activating effect on syntaxin-3 (STX-3)

DHA is deposited within the cerebral cortex at an accelerated rate during the last trimester of gestation and during the first two years after birth, rendering this phase of neuronal development particularly vulnerable to nutritional insufficiencies This early accelerated rate of DHA deposition coincides with the onset of myelination, a process that is sensitive to DHA accumulation and stores. Notably, animal data show that it is physiologically difficult to reverse the effects of early brain DHA depletion and that reduction of *n*-3 PUFAs in the diet negatively affects DHA concentrations within the brain Studies in non-human primates show that low DHA levels are associated with deficits in the visual system, in brain functions and in motor capabilities Furthermore, animal models provide solid evidence that the

consequences of dietary DHA deficiency are a high *n*-6 to *n*-3 PUFA ratio in brain fatty acid composition and deficiencies in learning and memory behaviors possibly due, in part, to negative impacts on neurite outgrowth and myelination.

Effects of DHA in Dementia

The levels of EPA, DHA, and total omega-3 PUFAs are significantly decreased in peripheral blood tissues of patients affected by dementia. Nine hundred mg/day of DHA supplementation for 24 weeks ameliorated memory in healthy older adults with age-related cognitive decline without side effects. In particular, DHA administration was associated with improvement in immediate and delayed verbal recognition memory scores, and Paired Associate Learning (PAL) scores. A 12-month fish oil (FO) supplementation with concentrated DHA in 36 low-socioeconomic-status elderly subjects with mild cognitive impairment (MCI) significantly ameliorated short-term and working memory, immediate verbal memory and delayed recall capability. The 12-month change in memory also significantly improved after treatment with good tolerance and minimal side effects. Eight hundred mg/day of DHA or/and 12 mg/day of lutein supplementation for 4 months significantly enhanced verbal fluency scores in unimpaired elder women. Memory scores and rate of learning significantly increased after the combined supplementation, without influencing mental processing speed, accuracy and mood.

Depression and Cognitive Function

EPA and DHA supplementation for 6 months in 50 people aged >65 years with MCI showed improvement in Geriatric Depression Scale (GDS) scores and mental health while verbal fluency and self-reported physical health ameliorated only in the DHA group . The administration of phosphatidylserine (PS) containing omega-3 long-chain PUFAs attached to its backbone (PS-DHA) for 15 weeks in non-demented elderly with memory complaints may significantly improve cognitive performance parameters such as immediate and delayed verbal recall, time to copy complex figures and learning abilities, especially participants with higher baseline cognitive status.

DHA in Alzheimer:

The apolipoprotein E ε4 (APOE4) allele identifies a unique population that is at significant risk for developing Alzheimer disease (AD). Docosahexaenoic acid (DHA) is an essential ω-3 fatty acid that is critical to the formation of neuronal synapses and membrane fluidity. Observational studies have associated ω-3 intake, including DHA, with a reduced risk for incident AD.

Several observational and clinical trials of ω-3 in the predementia stage of AD suggest that ω-3 supplementation may slow early memory decline in APOE4 carriers. Several mechanisms by which the APOE4 allele could alter the delivery of DHA to the brain may be amenable to DHA supplementation in predementia stages of AD. Evidence of accelerated DHA catabolism (eg, activation of phospholipases and oxidation pathways) could explain the lack of efficacy of ω-3 supplementation in AD dementia. The association of cognitive benefit with DHA supplementation in predementia but not AD dementia suggests that early ω-3 supplementation may reduce the risk for or delay the onset of AD symptoms in APOE4 carriers.

Rational of the formula:

1. Contains 125mg DHA/dose
2. Contains herbs like extract of Centella asiatica, Bacopa monneri and Convolvulus pluricaulis