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Rationale of Polyunsaturated Fatty Acids Supplementation in the Frame of the Magnocellular Theory of Dyslexia

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

In the last decades evidence has been collected that the depletion of the visual magnocellular population (a fast-conduction cellular system made of large ganglion neurons) plays a pathogenetical role in developmental dyslexia. Smaller size of the magnocells and reduction of their overall number in a proportion of disabled readers, in fact, are believed to hamper the visual processing of the written text.

Polyunsaturated fatty acids (PUFAs) are important structural parts of the cellular membrane and of the cytoskeleton, and are pivotal for the correct development and functioning of neurons. Magnocells are thought to be particularly vulnerable to PUFAs deficiency, due to the large extent of their plasma membrane: so, reduced availability of polyunsaturated fatty acids is argued to selectively affect the magnocellular population.

Indeed, PUFAs deficiency has been reported in a consistent proportion of disabled readers. This finding has led to hypothesize this deficiency may play a main role in the reading problems of patients by hindering the normal development of their magnocellular pathway.

Based on these assumption there is some evidence that dietary supplementation with a predefined combination of omega-3 and omega-6 fatty acids has a beneficial effect on the reading

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performance and behavior of dyslexics. Here the rationale for this line of intervention is reported. The conclusion is that supplementation of dyslexic children with PUFAs is worth to be considered, despite its effectiveness in improving their academic skills needs further clarification.

Keywords: Dyslexia; fatty acids; magnocellular; supplementation.

1. INTRODUCTION

Developmental dyslexia is a specific reading disability that affects approximately 4-10% of the scholar population [1,2]. A growing body of evidence is supporting the involvement of the visual function in the pathogenesis of this clinical condition. In the last decades, in fact, a number of dyslexic children is found to suffer from reduced sensitivity at high temporal and low spatial frequencies, reduced critical frequency fusion, defective motion perception, or increased visual persistence time. Since these functions are processed by the magnocellular (M-) pathway, it has been argued that in general patients have a defect in their magnocellular pool (see for example [3]).

The visual processing of an image, indeed, is provided by two distinct and parallel retinocortical pathways: the magnocellular (M-) or transient system and the parvocellular (P-) or sustained system. The M-system is made of larger ganglion cells, arranged in wider receptive fields. The P-system is made of small ganglion cells and arranged in receptive fields of small size. Magnocells make up about 5-10% of the ganglionar population, while parvocells constitute almost 90% of the retinal neurons. Like their anatomical features, also information carried by the M- and P-cells is different and basically complementary. Magnocells are mainly sensitive to contrast at low spatial and high temporal frequencies, and to moving stimuli. In turn, parvocells are mainly sensitive to contrast at high spatial and low temporal frequencies, to colors, and are in charge of the detection of fine details (visual acuity).

To date, there is no pharmacological therapy to cure the supposedly impaired M-visual pathway of dyslexics, so that visual training procedures (e.g [4,5]) and compensative interventions so far remain the only options to help them read better.

Yet, the integration with omega-3 and omega-6 polyunsaturated fatty acids, two substances that play an important role for health in general and promote the normal development of the child, is recently gaining consent to treat not only the lexical disability per se, but also the behavioral disorders frequently associated with this clinical condition.

Polyunsaturated fatty acids (PUFAs) are alkyl-chain fatty acids with two or more ethylenic double bonds. Based on the position of the double bonds along the carbon backbone, PUFAs are classified into two subgroups: omega-6 and omega-3 fatty acids.

Both types are essential for health. omega-3 alpha-linolenic acid and omega-6 linoleic acid cannot be synthesized by the organism [6], but must be obtained as part of the dietary intake, and are therefore called essential fatty acids (EFAs). From the essential fatty acids the organism synthesizes the omega-3 eicosapentaenioc (EPA) and docosahexaenoic acid (DHA), and the omega-6 gamma-linolenic acid (GLA), dihomogamma-linolenic acid (DGLA), and arachidonic acid (AA) (Table 1).

DHA and AA play a main role in the composition of the cellular membrane of the neurons [7].

The cellular membranes are made of a double layer of phospholipids, which a fatty acid linked to the second atom of the carbon chain (position SN-2) of the phospholipidic molecule. The membrane is continually repaired and renewed by a metabolic cycle driven by the cytosolic phospholipase A2 enzyme (PLA2). PLA2 takes off the fatty acid from the SN-2 position, turning it into its free form. The fatty acid is then renewed, and placed back in the same location on the phospholipidic molecule [8,9].

In addition, phospholipids are structurally involved in the formation of the cytoskeleton.

The renewal process requires large amounts of polyunsaturated fatty acids, in particular arachidonic, docosahexaenoic, diomogamma-linolenic, and eicosapentaenoic acid. In the fetus and in the early postnatal period these substances are provided by the mother respectively via the placenta and breast milk, whereas in adults PUFAs are derived, as reported, via synthesis from the precursors α-linolenic and linolenic acid.

Table 1. Polyunsaturated fatty acids

Ω-3 PUFAs	*Numeric Name*	*Ω-6 PUFAs*	*Numeric Name*
α-LINOLENIC [ALA] ↓	C18 :3n-3	LINOLENIC [LA] ↓	C18 :2n-6
		γ-LINOLENIC ACID [GLA]	C18 :3n-6
EICOSAPENTAENOIC [EPA] ↓	C20 :5n-3	DIHOMOGAMMA-LINOLENIC [DGLA] ↓	C20 :3n-6
DOCOSAHEXAENOIC [DHA]	C22 :6n-3	ARACHIDONIC [AA]	C20 :4n-6

2. POLYUNSATURATED FATTY ACIDS DEFICIENCY AND THE VISUAL SYSTEM

Polyunsaturated fatty acids (omega-3 and omega-6) make up a consistent proportion of the dry weight of the brain, and appear of outmost importance for its proper anatomo-functional development [10]. As a matter of fact, polyunsaturated fatty acids are pivotal for the maturation and functioning of the visual neurons, in particular of the ganglion cells. DHA and AA are responsible for the fluidity of the plasma membrane (DHA), help cells to reach their final size (AA and DHA), and contribute to correct cell signalling [11]; in turn, EPA and DGLA are essential for the regulation of the brain function [7].

Ganglion neurons, indeed, are very susceptible to omega-3 PUFAs deprivation, as suggested by their consistent omega-3 intake at the retinal level [12]. Such deprivation affects not only their soma [13] but also the myelin sheath wrapping their axons: reduced dietary intake of PUFAs (especially of DHA), in fact, is related to abnormal myelination of the visual pathway [14], functionally revealed in preterm newborn children by impaired visual evoked potentials [15].

Dietary depletion of docosahexaenoic acid is found to reduce the size of neurons in different brain regions of rats [16]. Among these neurons, magnocellular-type ganglion cells are thought to be particularly vulnerable to deficiency of polyunsaturated fatty acids, especially of DHA: the reason for their susceptibility is the extent of their membrane, so large as to require extra-amount of PUFAs for its structural turnover compared to the parvocells [10]. This hypothesis is indirectly supported by Zavodnik et al. [17], who found in their in vivo study that in presence of low concentrations of free fatty acids human red cells were smaller, and they increased in diameter as the concentration was raised.

Fatty acids linked to the phospholipidic molecules are important structural parts also of the cytoskeleton, a complex network of interlinking tubules and filaments located in the cytoplasm. The cytoskeleton is the second main factor determining the size and shape of the neurons [18].

As a matter of fact, phospholipids interact with the microtubules associated proteins (MAP), the main constituents of the cytoskeleton and responsible for its assembly and stability [19]. Phospholipidic deficiency following PUFA depletion, therefore, will affect not only the plasma membrane but also the cytoskeleton composition, eventually preventing the large ganglion cells from reaching their normal size.

In summary, PUFAs deficiency during the developmental age is expected to cause selective depletion of the large ganglion cells, that will appear restricted in size, making them resemble parvocells.

3. DEFECTIVE MAGNOCELLULAR STRUCTURE AND FUNCTION IN DYSLEXICS

A wide strand of psychophysical (e.g. [20-30]), electrophysiological [e,g. [31-37]), and functional imaging research [38-40] strongly suggests that the magnocellular pathway is abnormal in a consistent number of dyslexics. The defective functional pattern in patients would stem from abnormal cytologic structure, namely from reduced size of the M-cells. Livingstone and Galaburda confirmed this suggestion examining the lateral geniculate nucleus of 5 dyslexic (four males, one female, mean age: 34.2±13.7years) and 5 non-dyslexic subjects (all males, mean age: 40±11.2 years). The examined brains had been used by Galaburda in previous anatomical studies. Despite considerable overlapping of the measurements in the two groups, in patients the ventral (magnocellular) layers were disorganized and magnocells in average were smaller by 27% compared to the size of normal readers. On the contrary, no difference was found between dyslexics and controls in the histological structure of the dorsal (parvocellular) layers and in the size of the parvocells [31,41] (Fig. 1).

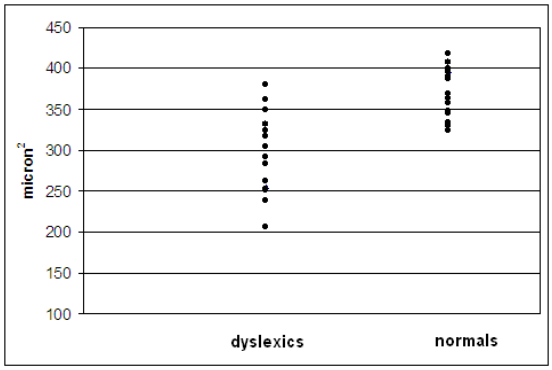

Fig. 1. Size of M- and P-cells of the lateral geniculate body in normal and dyslexic readers. (Data inferred from Livingstone et al. [31])

On the basis of the experimental evidence showing that defective M-pathway contributes to the reading disability, considered on the one hand that the M-population is impoverished in dyslexics, with the large ganglion neurons reduced in size, on the other that PUFAs are essential for the normal development of such neurons, it stands to reason that reduced amount of PUFAs may be related to the reading disability in dyslexic patients.

4. EVIDENCE FOR ABNORMAL METABOLISM OF POLYUNSATURATED FATTY ACIDS IN DYSLEXICS

The dietary intake of omega-3 (especially EPA and DHA) fatty acids is often deficient in western populations [42], and is often associated with lack of minerals and vitamins as Zinc, Magnesium, Vitamin B3, B6, and C [7]. In addition, habits like high assumption of saturated fatty acids, smoking, alcohol and coffee consumption further reduce PUFAs biodisponibility [43]. In subjects with allergic diathesis and in particular genetically-related defects of fatty acids metabolism, PUFAs depletion may be particularly relevant. This can be, indeed, the case of dyslexics.

Defective PUFAs metabolism due to abnormally high seric concentration of phospholipase A2, reduced incorporation of docosahexaenoic acid, arachidonic acid, and, ultimately, phospholipids into cell membranes has been documented in disabled readers [8,44-46]. Indeed, mild clinical signs of fatty acid deficiency, namely rough and dry skin and hair, weak and soft fingernails, dandruff, follicular keratosis, polydipsia, and pollakiuria, have been reported in these patients [47-49], and confirmed with biochemical testing in a dyslexic boy [47]. In turn, boys with lower plasma omega-3 polyunsaturated fatty acids showed more learning problems compared to those with higher concentrations [50], and the severity of these signs is found to correlate with the degree of reading and spelling disability [48, 49]. Notably, the relationship between PUFAs deficiency and reading performance was evident in males but not in females: this is not unexpected, as fatty acids needs in males is higher compared to females, as suggested by studies with animal models [51,52]. This discrepancy could explain the higher prevalence of reading disability in males (1.69 to 1, according to Miles et al. [53]) and, as suggested by Richardson et al. [48], it could be accounted for by beneficial hormonal effects (oestrogen in particular) on both synthesis and retention of PUFAs in females [54] (see [55] for a review).

In the overall dyslexic population studied by the group of Richardson, clear clinical signs of fatty acid deficiency was found in 32% of subjects, with no statistical difference between males and females (P>.05). In a previous study a consistently lower proportion (9%) was found in normal boys [56].

In summary, to quote Richardson et al.: "[..] fatty acid deficiency may be a factor in at least a substantial proportion of children with dyslexia, and accords very well with the single case of a dyslexic child reported so observantly by Baker [47]" [48].

5. POLYUNSATURATED FATTY ACIDS DIETARY SUPPLEMENTATION IN DYSLEXIA

As reduced amount of PUFAs seems involved in reading disability, dietary PUFAs supplementation should improve reading performance via normalization of the magnocellular structural deficiency in disabled readers.

Indeed, as recalled by Richardson and Phil [7], there is abundant anecdotal evidence of the effectiveness of PUFAs supplementation in treating dyslexia and related disorders: for example, Baker more than 30 years ago described the case of Michael, a dyslexic boy with the typical signs of fatty acid deficiency (dry and dull skin and hair, dandruff, soft and frayed fingernails, excessive thirsts and frequent urination) who showed substantial improvement in school performance after PUFAs dietary supplementation [47]. Yet, randomized controlled trials aimed at confirming the real benefit of these substances and at establishing what is the best formula and dosage are difficult to carry out.

In a double masked crossover investigation, the Oxford-Durham Study, 117 children aged between 5 and 12 years affected by developmental coordination disorder (DCD), a clinical condition that involves reading difficulty, were administered ω-3 (DHA and EPA) and ω-6 (GLA) fatty acids for three months [57].

Before treatment reading and spelling ages of patients were about 1 year below their chronological age. After 3 months of supplementation, mean reading and spelling age increased in the treated sample by 9.5 and 6.6 months, respectively, versus 3.3 and 1.2 months in the placebo group.

After the crossover, the improvement was confirmed in the treated group and reading age increased by 13.5 months in the ex-placebo subjects. In turn, spelling age improved by 6.2 months. The progress continued with the prosecution of the treatment during the following 3 months.

The authors highlighted that children supplemented with fatty acids made 3-4 times the expected normal gain in reading, and two times the expected gain in spelling. Importantly, they reported absence of side effects.

These results have been further confirmed in a group of 20 dyslexic children, who showed reading rate increase by 60% after 4 months of supplementation with DHA fish oil and evening primrose oil (rich in GLA and linoleic acid: [58]).

Not unexpectedly, the effect of supplementation with DHA in disabled readers would start at the lowest (retinal) level of the visual pathway: in fact, dark adaptation (scotopic vision), defective in dyslexics, is found to recover after dietary intake of DHA [59].

It should be noted, finally, that PUFAs dietary intake seems to affect positively not only the reading performance of dyslexic children, but also their ADHD-related symptoms: in disabled readers aged 8-12, 12 weeks-daily supplementation with EPA, DHA, GLA, AA, cis-linolenic acid, and (as antioxidant) vitamin E (delta-tocopherol), as well as thyme oil, has proven capable of significantly improving some comorbid ADHD features, that is psychosomatic problems, inattention, hyperactivity, impulsivity, and especially anxiety and cognitive problems, as computed at the Conners' Parent Rating Scale (CPRS-L) [60].

6. CONCLUSION

In conclusion, there is rational basis in support of polyunsaturated fatty acids supplementation as a safe approach to help dyslexics read better and succeed in their academic skills, even if the benefit of this type of treatment needs to be clarified. As highlighted by Richardson and Phil [7] not all the dyslexics will benefit from the treatment, but those who show evident signs of fatty acid deficiency are more likely candidates to substantial improvement. Notwithstanding, "a high dietary intake of HUFA is associated with many positive health benefits, so there should be little if anything to lose from trying such supplementation in the context of an appropriately balanced diet" [7].

Under a prevention perspective, it is worth recalling that a lack of the relevant dietary PUFAs in pregnant women could "[..] starve the fetus of the material needed to build neuronal processes." [10]. In addition, it is revealing what stated by Ahmad et al. [16], that is in the United

States human infant milk formulas are deficient in docosahexaenoic acid, and as docosahexaenoic acid deficiency reduces the size of the ganglion cells, infants fed with artificial milk may have smaller neurons compared to breast-fed children. According to what reported in literature and summarized in this paper, this would expose them to higher risk of developing reading disabilities and associated developmental disorders.

Finally, abnormalities of fatty acid metabolism seem to contribute not only to dyslexia but also to other developmental disorders like attention-deficit/hyperactivity disorder (ADHD) and dyspraxia (that in fact occurs in up to half of the dyslexic population: [7]), as well as schizophrenia and the autistic spectrum [61]: PUFAs supplementation benefit, therefore, could not be restricted to disabled readers but might even extend to this class of clinical conditions.

In conclusion, there is mounting evidence based on biochemical and behavioral studies of an involvement of fatty acid deficiency in dyslexia: based on this evidence, developing food supplements aimed at normalizing the intake of fatty acids in dyslexic children could be a promising therapeutic strategy to help them read better.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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