Research in Developmental Disabilities 35 (2014) 861–870

Contents lists available at ScienceDirect

Research in Developmental Disabilities

Review article

Clinical significance of neuropsychological improvement after supplementation with omega-3 in 8–12 years old malnourished Mexican children: A randomized, double-blind, placebo and treatment clinical trial

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ARTICLE INFO

Article history:
Received 6 October 2013
Received in revised form 7 January 2014
Accepted 9 January 2014
Available online 6 February 2014

Keywords:
Neuropsychology
Omega-3 supplementation
Malnourished children
Nutrition
Cognition

ABSTRACT

It has been shown that supplementation with omega-3 improves cognitive performance, especially in infants and toddlers, but it is unknown whether these results are effective in older malnourished children. The aims of this study, therefore, were to investigate the omega-3 supplementation effects in 8- to 12-year-old children and to know which neuropsychological functions improve after three months of intervention in a sample of Mexican children with mild to moderate malnutrition. This study was a randomized, double-blind, treatment and placebo study of 59 children aged 8–12 years who were individually allocated to 2 groups. The duration of the intervention lasted 3 months. Neuropsychological performance was measured at baseline and at 3 months. Results show that more than 50% of children in the treatment group had greater improvement in 11 of the 18 neuropsychological variables studied. Processing speed, visual-motor coordination, perceptual integration, attention and executive function showed improvement in more than 70% of the omega-3 supplemented children. This trial was registered at clinicaltrials.gov as NCT01199120.

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0891-4222/$ – see front matter
http://dx.doi.org/10.1016/j.ridd.2014.01.013

1. Introduction

Malnutrition is one of the most important nutritional issues during childhood because it is in the first years of life when growth is intensive and there is still ripeness of diverse organs. Therefore, the longer malnutrition lasts in a young child the consequences will be more serious (Pollitt, 2000). Malnutrition in children is the result of a poor diet, which is related to diverse biological, socioeconomic, and cultural factors (Rivera & Sepúlveda, 2003; Wachs, 2000; Zlotkin, 2006). At long term, malnutrition can result in damage of cognitive functions and academic performance (Grantham-McGregor, Cheung, Cueto, Glewwe, Richter, & Strupp, 2007). In addition, in socio-economical terms, poor countries are the most affected by the ravages of malnutrition, and this hampers their development (Branca, 2006).

The main nutritional deficiencies studied in children lie in the protein-energy, iron and essential fatty acids deficiency (Tofail et al., 2008; Walker, Chang, Powell, & Grantham-McGregor, 2005; Yehuda, Rabinovitz, & Mostofsky, 2006); and many of these researches tend to focus on the first two years of life, because it is believed that the brain develops intensively during those years (Benton, 2008). Nevertheless, researchers have recently concluded that brain maturation has not been completed at this stage and, in addition, its development is not uniform (Branca, 2006); on the other hand, brain development continues along infancy, during childhood, and up to adolescence (Ito, 2004; Romine & Reynolds, 2004). Therefore, cognitive and academic deficits in malnourished children during early childhood continue in late adolescence (Walker et al., 2005). Because of this, it is necessary to research nutrition issues during posterior ages (Benton, 2008).

Essential fatty acids (EFA) play an important role in learning faculties and behavior (Johnson, Ostlund, Fransson, Kadesjö, & Gillberg, 2009; Yehuda, Rabinovitz, & Mostofsky, 2005). Omega-3 (ω-3), is a particularly important EFA, its deficiency causes a significant reduction of catecholamine, which affects the transportation and usage of glucose by the brain (Yehuda et al., 2006). Omega-3 is composed by docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). DHA is a component of cerebral gray matter (Innis, 2007) particularly concentrated in synaptic nerve cells, where it seems to be involved in the signaling processes between neuronal cells (Youdim, Martin, & Joseph, 2000), controlling the activity of neurotransmitters and the neuronal growth factors (Yehuda, Rabinovitz, Carasso, & Mostofsky, 2002). Although the statement is controversial (Hirayama, Hamazaki, & Terasawa, 2004), it seems that DHA is crucial for normal cognitive functions (Sinn & Bryan, 2007). Any deviation of physiological levels of DHA is associated with cognitive impairment (Yehuda, Rabinovitz, & Mostofsky, 1999) and with some developmental disorders such as attention deficit disorder, autism, and motor problems (Johnson et al., 2009; Raz & Gabis, 2009; Richardson & Ross, 2000; Sinn & Bryan, 2007). Overall, these variables could impact learning performance (Branca, 2006).

Studies addressing Omega-3 supplementation to improve cognitive skills are focused in infants and in early childhood (Helland, Smith, Saarem, Saugstad, & Drevon, 2003; Innis, 2007; Merwe et al., 2013). In brief, these studies found that the supplementation improves the cognition in general. On the other hand, most of them use the statistical but not the clinical significance of participant improvements to compare supplemented and non-supplemented groups (Fontani, Corradeschi, Felici, Alfatti, Migliorini, & Lodi, 2005; Kennedy et al., 2009). This fact is becoming important to understand the clinical relevance of interventions (Atkins, Bedics, McGlinchey, & Beauchaine, 2005; Fethney, 2010; Hurst & Bolton, 2004; Man-Son-Hing et al., 2002).

In summary, most studies are characterized by: (1) making the intervention in children under 5 years of age (Innis, 2007; Parra-Cabrera, Moreno-Macias, Mendez-Ramirez, Schnaas, & Romieu, 2008); (2) not making a detailed assessment of the neuropsychological functions that continue to develop at later ages (Benton, 2008; Walker et al., 2005), and (3) not considering the clinical significance of results. Therefore, the objective of this paper is to investigate the ω-3 supplementation effects in 8- to 12-year-old children and to know which neuropsychological functions improve after 3 months of intervention in a sample of Mexican children with mild to moderate malnutrition. We hypothesize that the intervention group will get clinically relevant improvements in the functions related to memory and executive function.

2. Methods

2.1. Recruitment

Participants were recruited from two schools of low socioeconomic status in Ciudad Juarez, Mexico that were willing to assist with the study. Socioeconomic status (SES) was based on the II Conteo de Población y Vivienda (INEGI, 2005) data covering such areas as illiteracy, number of individuals living per room, etc., which are the foundation of an SES system. SES was classified as follows: 1, very low SES; 2, low SES; 3, middle SES; 4, high SES; 5, very high SES. According to the Plan de Desarrollo Urbano of Ciudad Juarez (2010), the residents of the two neighborhoods used for the study are of the low-SES group. The parents of children between 8 and 12 years were invited to attend a meeting at which the study procedures were explained and a written informed consent from the tutors and a verbal assent from their children were obtained. In the following days, anthropometric measurements were taken to establish their nutritional status. Once the number of malnourished children was established, a meeting with the parents was held to explain the project and ask for their consent.

2.2. Participants

The recruitment process yielded 59 children between 8 and 12 years. These children were attending 3rd to 4th year of elementary school. At the end, four children were not eligible because they did not fulfill the criteria or because they refused to participate. The remaining 55 malnourished children were assigned to the placebo (PlG) and treatment group (TxG), (25 PlG and 30 TxG) (see the flow chart in Fig. 1). There were 5 more subjects in the treatment group to avoid dropout. However the person who cataloged the sample wasn't involved in the application of the tests nor was she involved in the control of supplementations.

2.3. Inclusion and exclusion criteria

An inclusion criterion was the permission through informed consent from the primary caregiver. Exclusion criteria included the presence of neurological disease (epilepsy, brain injuries, any other neurological syndromes detected) and hormonal diseases (diabetes or thyroid-related diseases). Subjects who did not know how to swallow pills or who had ingested ω-3 supplement or any vitamin supplement in the last 6 months were also excluded.

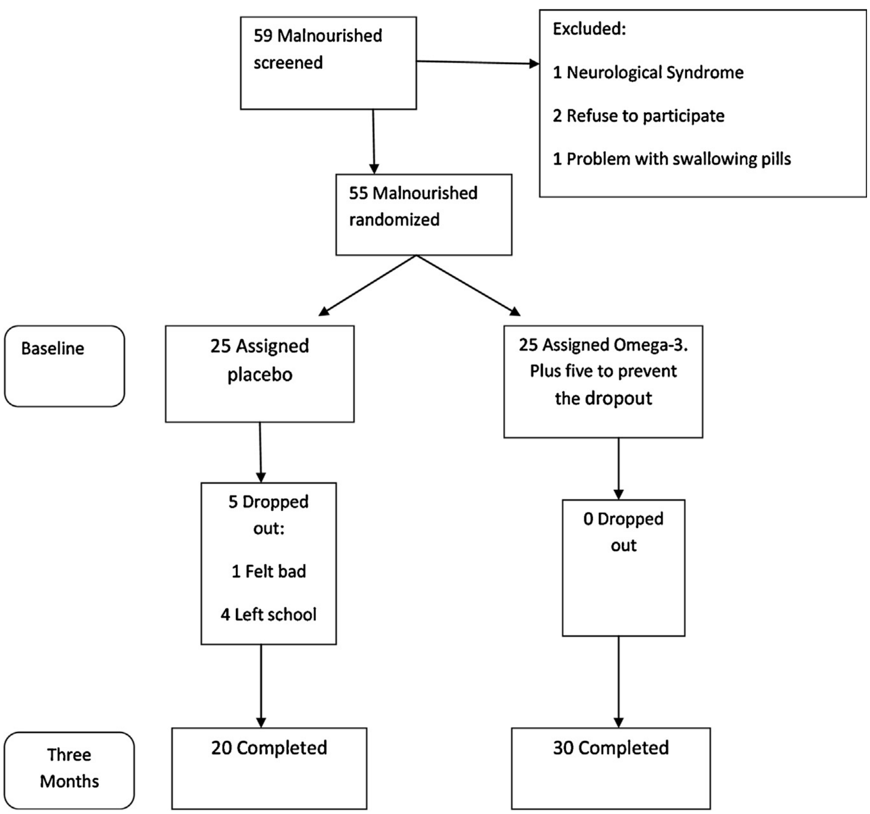

Fig. 1. Flow chart of the participants.

2.4. Study design

This was a randomized, double-blind, placebo-controlled and case-control study. The duration of the intervention was three months because it is the minimum time necessary to show effects on behavior and learning (Kairaluoma, Närhi, Ahonen, Westerholm, & Aro, 2009; Richardson & Puri, 2002), and it is also the duration that conforms to standards of other studies related to fatty acid supplementation. However, it is worth mentioning that, at present, there is no global consensus on the proper dosage and combination of fatty acids (Castro-González, Ojeda, Silencio, Cassis, Ledesma, & Pérez-Gil, 2004; Richardson & Montgomery, 2005). Therefore, the primary focus of the study was to compare the effects of parallel treatments for 3 months.

The entire battery was administered both at the beginning of the study (prior to the intervention) and at the end of it. The study was approved by the bioethics committee of the University Autonomous of Ciudad Juarez (UACJ). This trial was registered at clinicaltrials.gov as NCT01199120.

3. Intervention

The active treatment was a supplement containing fish ω-3 in gelatin capsules. The daily dose consisted of three capsules providing ω-3 (each capsule had 60 mg of DHA and 90 mg of EPA). Placebo treatment consisted of soybean oil capsules that looked similar to the active treatment.

Teachers administered two capsules daily (one early in the morning and another at lunchtime). The afternoon capsule and the weekend and holiday doses were administrated by the parents. Both parents and teachers were given a calendar to mark the supplement intake of each child; this calendar was delivered every two weeks. This information was completed with unused capsule counts.

4. Measures

4.1. Anthropometric measures

The anthropometric measurements that were used were core measures (weight and height) and anthropometric index (percentages of weight/age height/age and weight/height). The anthropometric measurements were performed according to specifications of the anthropometry manual from the National Council for Science and Technology (CONACYT), (Aparicio et al., 2004). The weight was determined by a Seca® electronic scale. The size was measured in a standing position, with the head placed so that the plane of Frankfurt was in a horizontal position; a Harpenden stadiometer was used to get these measurements. All subjects were wearing light clothes and no shoes during the anthropometric data collection phase. The reference standards for weight and height measurements were taken from the growth curve tables from the Center for Diseases Control (CDC, 2009). The cutoff points for malnourished group was 85–95% in height/age and 70–90% in weight/height (Waterlow, 1976).

4.2. Omega-3 consumption

The children's parents were asked to answer a questionnaire about the consumption frequency of food with a high content of ω-3, including most consumed products offered at the local markets. The consumption was registered by rations using the Mexican equivalents system. The content was quantified in grams of ω-3 per each 100 g of food source, in the case of fish, using the USDA lists as the source of information. High concentrations of omega-3 aliments frequently used have been quantified according to the reported products nutrimental labels. Omega-3 supplementation was also considered.

4.3. Neuropsychological measures

The neuropsychological test battery was selected to measure the following neuropsychological domains:

- Processing speed:
  - o *Symbol search*. Subtest of Wechsler Intelligence Scales for Children (WISC-IV), (Wechsler, 2007). Requires examinees to match symbols appearing in different groups.
  - o Visuoperceptive integration:
  - o *Embedded figures test*. This is a subtest of the Evaluación Neuropsicológica Infantil (ENI) (Matute, Roselli, Ardila, & Ostrosky-Solís, 2007). The child is asked to find a figure as quickly and as accurately as possible in a larger complex design in which it is embedded.
  - o *Visual closure*. This is a subtest of the ENI (Matute et al., 2007) and consists in complete visual patterns when only one or more parts of the object are presented.
- Visuomotor coordination:
  - o *Block design* (Wechsler, 2007). This test requires taking blocks that have all white sides, all red sides, and red and white sides, and arranging them according to a design.
  - o *TMT A* (Reitan, 1958). The subject in Part A must join with lines the numbered circles in consecutive form.

- Attention:
  - o *Letter cancellation* (Matute et al., 2007). The task consists of marking the letters "X" only when it is preceded by the letter A in a segment with different distracter letters as fast as possible.
- Memory:
  - o *Rey complex figure*. Examinees are asked to reproduce a figure, first by copying and then 3 min after from memory (Rey, 1987).
  - o *Word list* (Matute et al., 2007). Participants memorize a list of 12 words. The list was presented four times and participants were required to recall as many words as possible after each presentation. After half an hour, they were asked to recall the 12 original target words. Participants were then presented a list of distracter words and were asked to recall those. Following a filled delay, participants were again asked to recall, by categories, the original 12 target words.
- Language:
  - o *Semantic fluency* (*fruit*) (Matute et al., 2007). This task consists in saying all the names of fruits reminded by the subject in a minute period. The task excluded repeated words.
  - o *Comprehension instruction* (Matute et al., 2007). This measures the ability to comprehend the reading through a series of instructions.
- Executive function:
  - o *Matrix reasoning* (Wechsler, 2007). The purpose is to complete the picture matrix with any of the given solutions.
  - o Letter–number sequencing (Wechsler, 2007). This subtest of the WISC-IV consists in giving the subject a mixed set of numbers and letters orally and the subject has to complete two tasks. First, the subject has to arrange the numbers in ascending order orally and then arrange the letters in alpha order orally from the previously given set. This is a memory working test.
  - o *Stroop color and word test*. The test contains three lists. Children have to read words in the first list, say the name of colors in the second list, and say the name and color of the printed words as quickly and as accurately as possible in 45 s per task in third list (Golden, 2005).
  - o *TMT-B: Shifting*. In Part B, children must join circles with numbers and letters in alternative form (Reitan, 1958).

4.4. Academic measures

- *Absenteeism*. It was estimated by the number of times a student had not attended class in the bimester before-anterior and after-posterior the supplementation.
- *Academic performance*. Academic performance was the average score that children had in the subjects of Spanish, Mathematics, History and Geography, Science, and Civic Education.

5. Statistical analysis

All data was analyzed by the authors using the Statistical Package for Social Sciences (SPSS) version 15.

First, it was ensured that the groups were equally distributed among the demographic variables of the children and their mothers using the Chi-square test.

Then, a mixed ANOVA (2×2) was conducted with the variable "group" (treatment vs placebo group) and "moment" (pre-intervention vs post-intervention group) as factors. If the statistical significance was reached for main effects or interactions, Scheffé post hoc comparisons were conducted to analyze between-group differences. The neuropsychological variables were the dependent variables. Cohen's *d* was obtained for all that group comparisons.

Clinical significance was calculated for each participant using the individual effect size formula according to Wyrwich and Wolinsky (2000). After that, in order to know the amount of children that reached a large improvement according to Cohen's *d* criteria, each children was classified in three groups: (1) no improvement: if delta was between 0 and 0.5; (2) medium size improvement: if delta was between 0.51 and 0.8; and (3) large size improvement: if delta was bigger than 0.8. Chi-square analysis was conducted to determine the statistical significance of the improvement frequency in each group (Cohen, 1992).

6. Results

First, it was ensured that the groups were equally distributed in the demographic variables, of the children and their mothers. Results showed that there were no statistically significant differences in the age, IQ, absenteeism or academic performance of the children. Neither were statistically significant differences in the age, IQ, academic level, or economical status of their mothers (see Table 1).

After this, the questionnaire about the consumption frequency of food with high content of omega-3 revealed that only 8% of the children consumed a portion of fish two or more times a week, 39% one ration a week, 19% a ration every two weeks, and 34% a ration of once a month. 55% of this children consumed only canned tuna and 13% sardines in tomato sauce. The most consumed fish were tilapia, trout, hake, and salmon. The consumption frequency of aliments enriched with ω-3 was

Table 1
Sociodemographics characteristic.

	Treatment group (TxG)	Placebo group (PlG)	*F*/Chi	*p*
Age of mother (mean/SD)	31.80 (4.29)	32.47 (5.00)	0.225	0.637
Mother's education (%)			5.272	0.509
Elementary school	5	13.3		
Middle school	35	33.3		
High school	50	33.3		
Technical degree	5	16.7		
Bachelors degree	5	3.3		
Mother's IQ (mean/SD)	84.03 (9.70)	84.42(10.50)	0.330	0.568
Child IQ (mean/SD)	89.86(14.23)	93.80(19.12)	2.934	0.094
Child gender (%)			0.019	0.891
Female	34	24		
Male	26	16		
Total	42	58		
Child age (mean/SD)	9.37 (1.173)	9.08 (.985)	1.904	0.174
Social-economic status (%)				
Low	100	100		
Academic performance	7.328 (1.08)	7.496 (1.08)	0.028	0.867
Scholar absenteeism	2.00 (2.259)	2.521(3.475)	1.367	0.248
Physical activity performed (at least 1 h per week) (%)	100	100		

very low, only 10% of the evaluated children revealed consumption of two or more times a week, most of them in milk. These results confirm the necessity to supplement with ω-3 fatty acids.

6.1. Neuropsychological differences between groups, before and after the intervention

We studied if there were differences among the three groups before and after the intervention. The results show that only the TxG improved in Symbol search [$F = 8.27$; $p < 0.006$], Embedded figures [$F = 5.79$; $p < 0.020$], Visual closure [$F = 4.70$; $p < 0.035$], Block design [$F = 19.48$; $p < 0.000$], Stroop-color [$F = 7.885$; $p < 0.007$], and Stroop-color–word [$F = 4.514$; $p < 0.039$] and Matrix reasoning .045 [$F = 4.514$; $p < 0.039$] (see Table 2).

Sixty-three percent (12 of 19) of the neuropsychological measures showed moderate to big group effect size (Cohen's *d*) in TxG but only 10.5% did it in PlG (see Table 2).

6.2. Clinical significance of the individual improvement

We then proceeded to study the individual clinical improvement for each participant. Finally, in 11 of the 19 neuropsychological variables studied, more than 50% of the children in the treatment group had big improvement according to the criteria of Cohen ($d > 0.8$). Note that improvement was present in processing speed (Symbol search), coordination visuomotor (Block design), perceptual integration (Embedded figures), attention (Letter cancellation) and executive function (Letter and number sequencing and matrix reasoning) in more than 70% of the supplemented children (see Table 3).

7. Discussion

This study was designed to investigate the cognitive effects of omega-3 supplement in 8–12 years malnourished children using a comprehensive neuropsychological battery and considering the clinical significant of the results.

Our results show that omega-3 supplementation for three months has effects on some neuropsychological variables.

First, we found an improvement in visuoperceptual tests and processing speed. This result corroborates with several studies that have shown improvement in the visual processing areas after supplementation with omega-3 (Kirby, Woodward, & Jackson, 2010), even in a newborn's early months (Birch et al., 2010). However, our results show that this improvement can be achieved in the age window selected for this study. The improvement in processing speed could be explained by the effects that omega-3 has on the membrane of the neuron, the synapses and myelin (Yehuda et al., 2006). Similar studies found the same results with omega-3 supplementation (Cheatham, Nerhammer, Asserhoj, Michaelsen, & Lauritzen, 2011).

We have also found improvements in sustained attention, which is associated especially with the development of ADHD. In fact, previous studies have used omega-3 supplementation for improving attentional problems of children with ADHD disorder with mixed results (Benton, 2008; Raz & Gabis, 2009). Therefore, our results would support such intervention because, at least in our sample, we found that improvement. These results are also consistent with studies indicating that omega-3 is related to the increased availability of dopamine in the brain cortex (Yehuda et al., 2005).

Table 2
Differences in pre-post neuropsychological variables in treatment, placebo and control groups.

Domain	Variable	TxG (mean and SD)	PlG (mean and SD)				Effect	F	p	Pre-post delta	
			Pre	Post	Pre	Post				TxG	PlG
Processing speed		Symbol search	16.065 (4.135)	19.933 (4.456)	18.809 (6.104)	20.047 (5.267)	Pre Pos	31.21	0.000	0.901	0.217
							PP* Dx	8.27	0.006		
Visuoperceptual integration		Embedded figures	10.800 (1.936)	12.300 (1.822)	10.666 (2.456)	11.000 (2.569)	Pre Pos	14.31	0.000	0.798	0.867
							PP* Dx	5.79	0.020		
		Visual closure	4.233 (1.250)	5.200 (1.270)	3.809 (1.661)	4.142 (1.621)	Pre Pos	19.812	0.000	0.767	0.202
							PP* Dx	4.70	0.035		
Visuoconstructive integration		Block design	21.500 (8.240)	28.333 (8.138)	22.428 (10.254)	22.571 (9.303)	Pre Pos	21.182	0.000	0.834	0.014
							PP* Dx	19.482	0.000		
		TMT-A	93.766 (47.342)	76.433 (44.961)	84.684 (26.119)	75.842 (33.992)	Pre Pos	7.025	0.011	0.375	0.294
							PP* Dx	0.739	0.394		
Attention		Letter cancellation	20.333 (7.702)	23.733 (6.329)	20.095 (8.383)	21.857 (7.882)	Pre Pos	16.995	0.000	0.484	0.216
							PP* Dx	1.71	0.197		
ENI: verbal memory		Verbal immediate recall	22.166 (8.530)	27.700 (5.627)	21.381 (5.142)	25.285 (5.857)	Pre Pos	20.507	0.000	0.781	0.709
							PP* Dx	0.611	0.438		
		Verbal free recall	6.700 (2.561)	8.166 (1.743)	7.000 (2.509)	7.619 (1.774)	Pre Pos	8.538	0.005	0.681	0.289
							PP* Dx	1.410	0.241		
		Verbal clue recall	6.833 (2.422)	8.533 (1.851)	6.904 (2.071)	8.142 (1.681)	Pre Pos	23.525	0.000	0.795	0.659
							PP* Dx	0.581	0.449		
		Verbal recognition	20.733 (3.268)	22.066 (1.460)	21.666 (1.425)	21.714 (2.028)	Pre Pos	3.523	0.066	0.561	0.027
							PP* Dx	3.054	0.087		
REY: visual memory		Visual immediate recall	11.433 (6.508)	14.700 (7.355)	11.023 (6.664)	10.809 (5.801)	Pre Pos	2.283	0.137	0.471	0.034
							PP* Dx				
Language		Fruit	8. 166 (1.782)	8.666 (2.287)	9.733 (2.362)	9.619 (1.657)	Pre Pos	12.285	0.001	0.237	0.483
							PP* Dx	0.77	0.386		
		Comprehension instruction	7.483 (1.600)	8.283 (1.498)	7.857 (1.074)	8.428 (1.154)	Pre Pos	20.534	0.000	0.516	0.512
							PP* Dx	0.570	0.454		
Executive function	Reasoning	Matrix reasoning	11.966 (4.139)	14.033 (3.782)	12.523 (3.515)	13.095 (3.448)	Pre Pos	13.203	0.001	0.521	0.164
							PP* Dx	4.24	0.045		
	Working memory	Letter–number sequencing	9.633 (5.404)	12.366 (3.498)	9.523 (4.812)	10.809 (4.308)	Pre Pos	14.085	0.000	0.612	0.282
							PP* Dx	1.83	0.183		
	Shifting	TMT-B	190.037 (74.369)	171.888 (55.339)	184.294 (85.866)	173.058 (88.387)	Pre Pos	1.175	0.285	0.279	0.129
							PP* Dx	0.065	0.800		
	Inhibition	Stroop word	60.300 (14.506)	64.733 (13.449)	56.66 (15.589)	59.000 (16.136)	Pre Pos	2.668	0.109	0.316	0.148
							PP* Dx	0.257	0.614		
		Stroop color	44.566 (10.624)	48.533 (9.821)	43.523 (9.790)	40.857 (9.079)	Pre Pos	0.303	0.585	0.388	0.282
							PP* Dx	7.885	0.007		
		Stroop color–word	22.566 (5.411)	27.260 (6.979)	23.333 (5.121)	24.381 (4.609)	Pre Pos	11.332	0.001	0.757	0.215
							PP* Dx	4.514	0.039		
Abssenteims			2.000 (2.259)	1.366 (1.629)	2.476 (3.641)	1.619 (1.283)	Pre Pos	4.344	0.042	0.328	0.348
							PP* Dx	0.098	0.756		
Academic performance			7.328 (1.087)	7.900 (0.944)	7.496 (1.083)	7.919 (1.163)	Pre Pos	27.717	0.000	0.563	0.376
							PP* Dx	0.628	0.432		

Note: Results are natural punctuation of each test. The increased of the scores indicating improved ability, except in TMT-A and TMT-B where the reduction of score is synonymous of improved performance. PP*Dx = interaction effect between neuropsychological assessment time (pre vs post) and TxG vs PlG variables

Table 3
Means, standard deviations and % of children by groups with delta > 0.8 in each neuropsychological variables.

Domain		Variable	TxG (mean and SD)	PlG (mean and SD)	% of children with delta > 0.8	
					TxG % (*n*)	PlG % (*n*)
Processing speed		Symbol search	0.935 (0.902)	0.202 (0.369)	89.5 (17)	10.5 (2)
Visuoperceptual integration		Embedded figures	0.774 (0.865)	0.135 (0.709)	82.4 (14)	17.6 (3)
		Visual closure	0.773 (0.903)	0.200 (0.515)	85.7 (18)	14.3 (3)
Visuoconstructive integration		Block design	0.829 (0.728)	0.013 (0.404)	100 (17)	0 (0)
		TMT-A	0.366 (.804)	0.338 (0.957)	33.3 (1)	66.7 (2)
Attention		Letter cancellation	0.441 (0.691)	0.278 (0.396)	85.7(6)	14.3 (1)
ENI: verbal memory		Verbal inmediate recall	0.648 (0.947)	0.759 (1.178)	65 (13)	35(7)
		Verbal free recall	0.572 (1.093)	0.246 (0.801)	58.8 (10)	41.2 (7)
		Verbal clue recall	0.701 (1.000)	0.597 (0.777)	68.2 (15)	31.8 (7)
		Verbal recognition	0.408 (0.951)	.033 (1.075)	70 (7)	30 (3)
REY: visual memory		Visual inmediate recall	0.501 (1.190)	0.032 (0.906)	66.7 (8)	33.3 (4)
		Fruit	0.038 (0.559)	0.124 (0.342)	0 (0)	0 (0)
Language		Comprehension instruction	0.500 (0.664)	0.532 (0.990)	47.4 (9)	52.6(10)
Executive function	Reasoning	Matrix reasoning	0.499 (0.591)	0.103 (0.488)	87.5 (7)	12.5(1)
	Working Memory	Letter–number sequencing	0.505 (0.833)	0.267 (0.479)	75 (6)	25 (2)
	Shifting	TMT-B	0.244 (1.090)	0.130 (1.131)	50 (3)	50 (3)
	Inhibition	Stroop word	0.305 (1.089)	0.149 (0.804)	78.6 (11)	21.4 (3)
		Stroop color	0.373 (0.840)	0.272 (0.744)	80 (8)	20 (2)
		Stroop color–word	0.856 (1.259)	0.204(0.847)	73.7 (14)	26.3 (5)
Academic performance			0.526 (0.591)	0.390 (0.640)	N/A	N/A

Note: TxG, treatment group; PlG, placebo group. Results are natural punctuation of each test. The increased of the scores indicating improved ability, except in TMT-A and TMT-B where the reduction of score is synonymous of improved performance.

In addition, we found a significant improvement in the update component of executive function such as abstract reasoning and working memory. These results are consistent with previous studies that have found improvements in these functions after supplementation, even though not at this age. However, we hypothesized that a high number of children would improve in the treatment group because the intervention was conducted in this period for this particular function. In addition, the findings on the role of omega-3 on the enhanced availability of neurons in the cortex and their role with the increased availability of dopamine as well may explain these findings (Yehuda et al., 2006).

Like many authors, we found no differences in any of the memory variables (Muthayya et al., 2009). This could show the specificity of the effects of omega-3 and would suggest not using global measures of cognitive performance. Moreover, this effect is not dependent on improved processing speed as memory tests measure precision, not speed. However, these results do not support our initial hypothesis that expected an improvement in memory due to previous findings on the role of omega-3 in the number of neurons in the hippocampus. Although this improvement has occurred in the intervention group, this was also evident in the other groups, showing that memory is more sensitive to external stimulation to the effect of omega-3.

As far as we know, this is the first study of omega-3 supplementation where the magnitude of change is considered for each participant. We found large changes in the neuropsychological variables in malnourished children supplemented with omega-3 that were not observed in placebo malnourished children. These results show significant increases over 70% of children in the supplemented group and throw light on the clinical significance beyond the statistics relevance. Although no previous studies with only omega-3 supplementation in malnourished children aged 8–12 have been carried out, a similar study found no significant improvement postoperatively (Muthayya et al., 2009). The difference in design, supplements, and neuropsychological tests do not allow comparisons between these two studies.

However, these results may be limited by three factors. First, all children in the sample belonged to the same socioeconomic status. Second, the serum levels for measuring PEM status were not used in this study because children with severe malnutrition were excluded. Third, the ratio of w-6/w-3 was not measured.

8. Conclusions

In summary, the results of our RCT study show a specific effect of supplementation with omega-3 in processing speed, visuoperceptive capacity, attention, and the updating component of executive function. These improvements are clinically significant and it has been obtained in 8–12 year children after controlling for most of the child and mother confounders.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The authors would like to thank the children, parents and principals of the schools where the project was developed, and the technicians who participated in the data recollection process.

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