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Membrane fatty acids, reading and spelling in dyslexic and non-dyslexic adults

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Abstract Increasing evidence implicates functional deficiencies or imbalances of omega-3 and omega-6 fatty acids in dyslexia. The associations between literacy skills and omega-3 and omega-6 fatty acid status were examined. 32 dyslexics and 20 controls completed standardised tests of reading and spelling and gave venous blood samples for analysis of the polar lipid fatty acid composition of red blood cell (RBC) membranes. Relationships between literacy skills and omega-3 and omega-6 concentrations were examined using rank-order correlations. Better word reading was associated with higher total omega-3 concentrations in both dyslexic and control groups. In dyslexic subjects only, reading performance was negatively associated with the ratio of arachidonic acid/eicosapentaenoic acid (ARA/EPA) and with total omega-6 concentrations. There were no significant differences in membrane fatty acid levels between the dyslexic and control subjects. However, the finding that omega-3 status was directly related to reading performance irrespective of dyslexia supports a dimensional view of this condition, and our results also suggest that it is the omega-3/omega-6 balance that is particularly relevant to dyslexia.
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1. Introduction

Developmental dyslexia refers to a neurodevelopmental syndrome with a constitutional basis, defined by specific difficulties in learning to read and write, diagnosed when the achievement in these domains falls substantially below the level expected for the subject's age, intelligence and education (APA, 2000). Dyslexia affects between 5% and 10% of the population, and is more common in males than females (Miles, 1993; Shaywitz, 1998). It also involves more than just reading difficulties and associated phonological impairments. Other core features include abnormalities in visual and auditory processing (Stein, 2001; Talcott et al., 2002; Wright et al., 2000), motor coordination difficulties (Nicolson et al., 2001), problems with orientation, direction and sequencing (Miles, 1993), and a particularly uneven profile of cognitive strengths and weaknesses.

There is increasing evidence that functional deficiencies or imbalances of omega-3 and omega-6 highly unsaturated fatty acids (HUFA) may play a role in dyslexia and related developmental conditions, such as attention-deficit hyperactivity disorder (ADHD), dyspraxia and autism (Richardson et al., 2003; Richardson and Ross, 2000), as well as some adult psychiatric disorders (Haag, 2003; Peet, 2003). Dyslexic individuals show an elevated frequency of physical

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signs consistent with essential fatty acid deficiency, such as excessive thirst, frequent urination, dry hair and skin, soft, brittle nails and follicular keratosis, and these have also been related to the severity of dyslexic symptoms (Baker, 1985; Richardson et al., 2000, 1999; Taylor et al., 2000). Low blood concentrations of omega-3 and sometimes omega-6 HUFA have been reported in both ADHD (Stevens et al., 1995) and autism (Bell et al., 2004). To date, however, there have been few biochemical studies of blood fatty acids in dyslexia. Fatty acid deficiency on objective testing was described in a single case study of a dyslexic child (Baker, 1985) but no details were reported. Other biochemical evidence is more indirect. Increased concentrations of a cytosolic phospholipase A_2 (PLA_2) enzyme, which is responsible for an excessive turnover and potential loss of HUFA from membrane phospholipids, were reported in dyslexic adults compared with controls (MacDonell et al., 2000), and one early study using cerebral 31-Phosphorus Magnetic Resonance Spectroscopy (31-P MRS) found evidence consistent with membrane lipid abnormalities in dyslexic adults compared with controls (Richardson et al., 1997). Preliminary evidence from treatment trials suggests potential benefits from fatty acid supplementation in dyslexia and related conditions (Richardson, 2004). A small study of dyslexic children showed reductions in a range of ADHD symptoms after supplementation with omega-3 fatty acids (Richardson and Puri, 2002). Furthermore, significant improvements in reading, spelling, and behaviour after supplementation were reported in a larger treatment trial of dyspraxic children (Richardson and Montgomery, 2005).

Omega-3 and omega-6 HUFA are crucial for normal brain development and function, and are recognized as essential nutrients because they cannot be synthesized *de novo* in sufficient quantity, and must be delivered pre-formed from dietary sources (Yehuda et al., 1999; Uauy et al., 2001). However, many diets consumed in the developed world contain sub-optimal levels of key HUFAs. In addition, it has been suggested that the biological predisposition to some neurodevelopmental and psychiatric disorders may include abnormalities of HUFA metabolism, which may require increased dietary intake of omega-3 and/or omega-6 fatty acids in these subjects (Horrobin et al., 1995).

Although the evidence for an association between dyslexia and abnormal fatty acid metabolism is growing, the core difficulties in reading and spelling have so far received little attention in this respect. The aim of this study was therefore to examine associations between literacy skills and omega-3 and omega-6 HUFA status from analyses of blood lipid profiles in dyslexic and non-dyslexic adults.

2. Experimental procedures

All subjects (32 dyslexic adults and 20 matched controls) completed a brief adult dyslexia screening test (Richardson et al., 1999) and a battery of psychometric measures widely used in the assessment of dyslexia. Six subtests from the Wechsler Adult Intelligence Scales (WAIS) were used; four assessing general ability: Similarities, Vocabulary, Block Design, Picture Arrangement; and two working memory: Digit Span and Digit Symbol (Wechsler, 1981). Literacy skills were measured with the Wide Range Achievement Test (WRAT) Word Reading, Spelling (Wilkinson, 1993). Fasting venous blood samples were collected, separated into red blood cell (RBC) and plasma fractions and stored at -80 °C within 1 h.

Exclusion criteria for all subjects were: low general ability (IQ pro-rated from WAIS Similarities, Vocabulary, Block Design and Picture Arrangement <80), any neurological, psychiatric or other major medical disorder, or any use of fatty acid supplements within the last 6 months. Dyslexic subjects were selected according to the following criteria: 1) previous history/assessment; 2) discrepancy between general ability (pro-rated IQ) and reading of at least 1.5 SD; and 3) positive indicators including particular impairments in auditory working memory (Digit span), and a score of more than 8 on the adult dyslexia screening checklist. Controls were selected for no history of reading difficulties, reading and spelling within the normal range, and a score of less than 8 on the adult dyslexia screening checklist. The study was approved by the Oxfordshire Psychiatric Research Ethics Committee. All subjects gave written informed consent before taking part in the study.

Subjects were asked to fast overnight before venous blood samples (20 ml) were collected into vacutainers containing ethylene diamine tetra-acetic acid (EDTA) and centrifuged at 4 °C (4000 $\times g$, 8 min) to separate erythrocytes from plasma. The samples were stored at -80 °C, encoded and sent to the Lipid Nutrition Group, University of Stirling, where measurements were carried out by workers blind to subjects' identity or scores on the psychometric measures. Samples of RBC were extracted by a variation of the Bligh and Dyer's (1959) method, the polar lipid fraction isolated by thin-layer chromatography. Fatty acid methyl esters were prepared by acid-catalysed transesterification of total lipids according to the

Table 1 Subject details

Sex		Control $N=20$		Dyslexic $N=32$		Sig.(2-tailed)
		11 M, 9 F		11 M, 21 F		
		Mean	SD	Mean	SD	
Age (years)		34.6	(9.4)	32.4	(10.2)	ns
General ability	Similarities	13.8	(2.7)	12.6	(2.9)	ns
	Vocabulary	14.1	(3.1)	13.0	(3.4)	ns
	Picture arrangement	11.6	(2.1)	10.6	(3.1)	ns
	Block design	13.6	(2.3)	12.0	(2.8)	ns
Short-form IQ		116.3	(7.9)	111.5	(12.6)	ns
Literacy skills	Word reading	112.8	(5.9)	96.0	(16.3)	$p<0.0001$
	Spelling	106.9	(9.8)	91.0	(19.1)	$p<0.0001$
Working memory	Digit span	12.0	(3.2)	8.4	(3.2)	$p<0.001$
	Digit symbol	12.8	(2.6)	10.4	(2.4)	$p<0.003$

Table 2 RBC membrane fatty acid levels in control and dyslexic groups

	Control		Dyslexic		M—W
	Mean	SD	Mean	SD	(Sig.)
Total *n*—3	9.24	(1.43)	9.32	(2.28)	0.641
18:3 *n*—3	0.19	(0.05)	0.20	(0.04)	0.213
20:5 *n*—3 (EPA)	1.03	(0.41)	1.07	(0.63)	0.431
22:5 *n*—3	2.53	(0.28)	2.55	(0.25)	0.936
22:6 *n*—3 (DHA)	5.31	(1.07)	5.33	(1.64)	0.860
Total *n*—6	29.33	(1.76)	29.30	(2.49)	0.785
18:2 *n*—6	10.31	(0.91)	10.20	(1.19)	0.459
20:3 *n*—6	1.58	(0.34)	1.73	(0.42)	0.177
20:4 *n*—6 (ARA)	14.08	(1.01)	13.97	(1.50)	0.923
22:4 *n*—6	2.59	(0.51)	2.66	(0.54)	0.228
22:5 *n*—6	0.41	(0.13)	0.40	(0.12)	0.872
Total mono	17.14	(1.01)	17.11	(0.85)	0.834
18:1 *n*—9	12.60	(0.94)	12.50	(0.69)	0.847
18:1 *n*—7	1.46	(0.14)	1.46	(0.16)	0.653
Total saturates	37.56	(0.74)	37.54	(0.55)	0.936
14:00	0.30	(0.07)	0.29	(0.06)	0.546
16:00	20.24	(0.81)	20.07	(0.75)	0.343
18:00	14.04	(0.64)	14.20	(0.55)	0.254
n—6/*n*—3 ratio	3.27	(0.69)	3.37	(1.01)	0.664
AA/EPA ratio	15.81	(6.41)	17.04	(7.90)	0.431
LA/ALA ratio	56.70	(12.79)	53.18	(11.53)	0.143

Values are expressed as mg/100 mg of total phospholipids: mean, SD.

method of Christie (1982). Fatty acid methyl esters were separated and quantified by gas—liquid chromatography (Carlo Erba Vega 8160, Milan, Italy) using a 60 m × 0.32 mm i.d. capillary column (ZB-Wax, Phenomenex, Macclesfield, U.K.) and on-column injection. Hydrogen was used as carrier gas and temperature programming was from 50 °C to 150 °C at 40 °C min^{-1} and then to 225 °C at 2.0 °C min^{-1}. Individual methyl esters were identified by comparison with known standards. Data were collected and processed using the Chromcard for Windows (version 1.19) computer package (Thermoquest Italia S.p.A., Milan, Italy).

Group differences (dyslexic/control) and the relationships between literacy skills and omega-3 and omega-6 HUFA concentrations (as % of RBC polar lipids) were examined using non-parametric tests (Mann—Whitney U test and rank-order correlations; Spearman's rho, 2-tailed).

3. Results

The two groups were well-matched for age and general ability, as shown in Table 1, but as expected, the dyslexic group had significantly lower scores on measures of literacy skills (WRAT reading and spelling), and working memory tasks (WAIS Digit Span and Digit Symbol). There were no significant differences between the groups (dyslexic/control) by age (MW U, $z = -0.934$, $p = 0.351$), or by sex (Chi square = 0.032, $p = 0.510$).

3.1. Group comparisons

The results of the fatty acid analysis are shown in Table 2. There were no significant differences between the dyslexic and control group on any of the RBC fatty acid measures.

3.2. Reading performance and RBC total omega-3 fatty acids

Total omega-3 HUFA concentrations correlated positively with reading performance in the whole sample, as well as in

Table 3 Correlations: literacy skills and omega-3 (whole sample $N = 52$ and by group)

	Whole sample $N = 52$		Control $N = 20$		Dyslexic $N = 32$	
	Reading	Spelling	Reading	Spelling	Reading	Spelling
18:3 *n*—3	0.12	0.07	0.14	−0.05	0.42*	0.38
18:4 *n*—3	0.29*	0.17	0.36	0.04	0.20	0.18
20:4 *n*—3	−0.01	−0.05	0.02	−0.11	0.28	0.12
20:5 *n*—3	0.26	0.15	0.12	0.05	0.33	0.15
22:5 *n*—3	0.08	−0.02	0.04	−0.14	0.15	0.01
22:6 *n*—3	0.35*	0.30*	0.56*	0.50*	0.33	0.24
Total *n*—3	0.36**	0.28*	0.49*	0.38	0.37*	0.26

Spearman's rho * $p < 0.05$, ** $p < 0.1$.

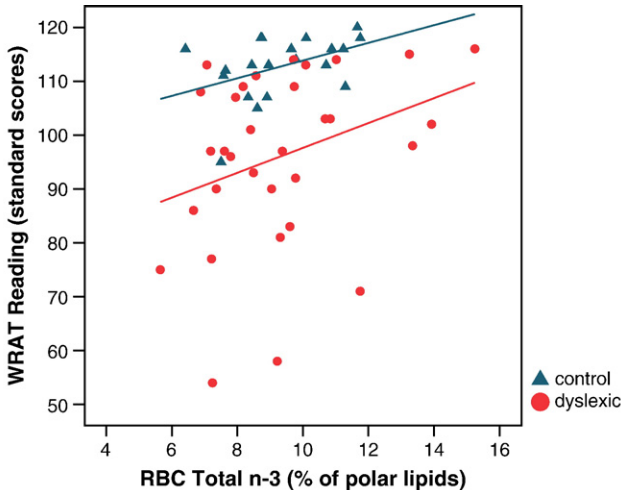

Figure 1 Correlation of reading performance by total omega-3 by group.

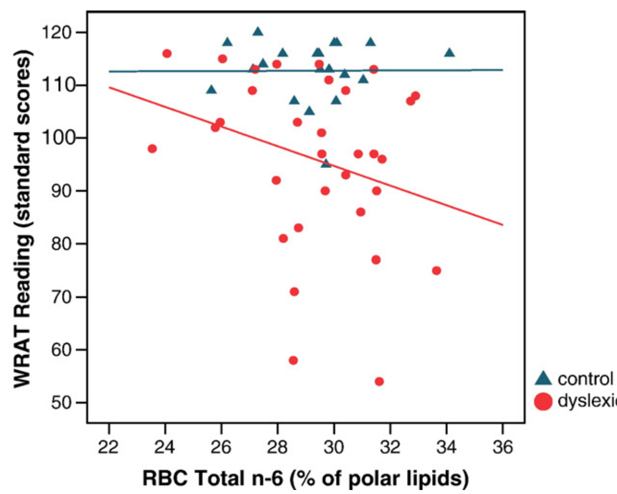

Figure 2 Correlation of reading performance by total omega-6 by group.

each group. Spelling correlated with total omega-3 HUFA concentrations in the whole sample, but not in the separate groups (see Table 3, Fig. 1).

3.3. Reading performance and RBC total omega-6 fatty acids

Total omega-6 HUFA concentration did not reveal significant correlations with reading or spelling performance. Adrenic acid correlated negatively with reading in the whole sample; this was also the case for the dyslexic group only. There was a trend-level negative correlation between total omega-6 HUFA concentration and reading in the dyslexic group (see Table 4, Fig. 2). There were no significant relationships between any of the RBC omega-6 fatty acid measures and spelling.

3.4. Reading performance and ratio of omega-6/omega-3

Total omega-3 fatty acid concentrations were *positively* correlated with reading performance in both dyslexic and control subjects, whereas total omega-6 concentrations showed a slight *negative* correlation with reading in dyslexic subjects only. Total omega-6 and omega-3 fatty acids showed strong inverse relationships in this sample, particularly in dyslexic subjects (control, rho = −0.72, $p < 0.001$; dyslexic, rho = −0.92, $p < 0.00001$). The relationships of ratios of omega-6 and omega-3 fatty acids with reading were therefore examined.

The ratio of omega-6/omega-3 fatty acids correlated negatively with reading at trend level in dyslexic but not control subjects. The ratios of both LA/ALA and ARA/EPA showed a negative correlation with reading performance in the dyslexic group (see Table 5, Figs. 3—5).

4. Discussion

In this study we investigated the associations between literacy skills and omega-3 and omega-6 fatty acid status in dyslexic and non-dyslexic adults. RBC membrane lipid total omega-3 HUFA concentrations were positively correlated with reading performance, in both dyslexic and control groups. There was also a trend for negative correlation between total omega-6 HUFA concentration and reading, but this was significant only within the dyslexic group. Total omega-6 and omega-3 fatty acid concentrations showed a strong inverse relationship in this sample, and particularly in dyslexic subjects. Hence the ratio of omega-6/omega-3 fatty acids, as well as more specifically the ratios of LA/ALA and of ARA/EPA, correlated negatively with reading in dyslexic but not strongly in control subjects.

In order to make sure that the study results were not due to differences in dietary intake within the sample, we exa-

Table 4 Correlations: literacy skills and omega-6 (whole sample $N = 52$ and by group)

	Whole sample $N = 52$		Control $N = 20$		Dyslexic $N = 32$	
	Reading	Spelling	Reading	Spelling	Reading	Spelling
18:2 *n*−6	0.11	0.14	0.44	0.31	−0.12	0.03
18:3 *n*−6	−0.07	−0.08	−0.09	0.00	−0.05	−0.12
20:3 *n*−6	−0.23	−0.17	0.04	−0.01	−0.22	−0.15
20:4 *n*−6	−0.26	−0.16	−0.34	−0.18	−0.29	−0.16
22:4 *n*−6	−0.34*	−0.25	−0.14	−0.04	−0.42*	−0.33
22:5 *n*−6	−0.16	−0.05	−0.05	0.01	−0.25	−0.02
Total *n*−6	−0.23	−0.15	0.02	0.06	−0.34	−0.21

Spearman's rho $*p < 0.05$, $**p < 0.1$.

Table 5 Correlations: literacy skills and omega-6/omega-3 ratios (whole sample $N=52$ and by group)

	Whole sample $N=52$		Control $N=20$		Dyslexic $N=32$	
	Reading	Spelling	Reading	Spelling	Reading	Spelling
$n-6/n-3$ ratio	−0.32*	−0.24	−0.32	−0.22	−0.34	−0.23
AA/EPA ratio	−0.28*	−0.18	−0.18	−0.11	−0.35*	−0.17
LA/ALA ratio	−0.06	−0.03	0.13	0.29	−0.52**	−0.39*

Spearman's rho *$p<0.05$, **$p<0.1$.

mined the relationships between reading and the intake of some foods. There were no relationships between reading performance and fish intake, but reading correlated negatively with dietary intake of sweets, and positively with intake of nuts. Furthermore, there were also no differences in reading, fatty acid concentrations or omega-6/omega-3 ratios between the vegetarian and non-vegetarian participants.

However, a causal link between low cellular omega-3 HUFA and poor reading cannot be established from these data, which are purely correlational. Nonetheless, the results are consistent with the proposal that omega-3 HUFA concentrations may play an important role in reading performance. Of particular interest is that the correlation between omega-3 status and reading was statistically significant regardless of the diagnosis of dyslexia, which would support a dimensional view of this condition. No significant group differences in RBC HUFA were observed. Thus, our findings suggest that imbalances in omega-6/omega-3 ratios might be especially relevant to subjects with dyslexia.

There were no differences on any of the RBC fatty acid measures or in reading and spelling by sex. Although there was a similar proportion of males and females in both groups, the subject numbers were too small to permit a proper investigation of this issue. However, there is evidence that vulnerability to fatty acid deficiency may be increased in males due to hormonal effects on the synthesis and retention of HUFA (Huang and Horrobin, 1987; Marra and de-Alaniz, 1989). As sex differences may influence fatty acid metabolism (de Alaniz and Marra, 2003), this issue would be worthy of investigation in the future.

Possible mechanisms by which low omega-3 status might impair reading are many, given the importance of omega-3 HUFA EPA and DHA to so many different aspects of brain structure and function, including sub-optimal visual processing abilities. These results are supported by a previously reported finding of high concentrations of arachidonic acid (ARA) associated with visual symptoms when reading in dyslexia (Cyhlarova et al., 2004).

If low omega-3 HUFA status does in any way contribute to poor reading performance, then optimising omega-6/omega-3 HUFA balance by means of a omega-3 HUFA supplementation may produce beneficial results. To gain a more precise understanding of the effects of omega-3 HUFA treatment, the results of this study need to be confirmed by blood biochemical analysis before and after supplementation. A

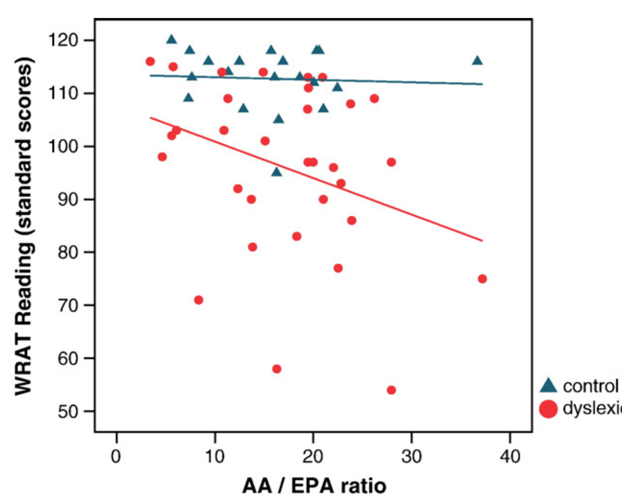

Figure 4 Correlation of reading by ARA/EPA ratio by group.

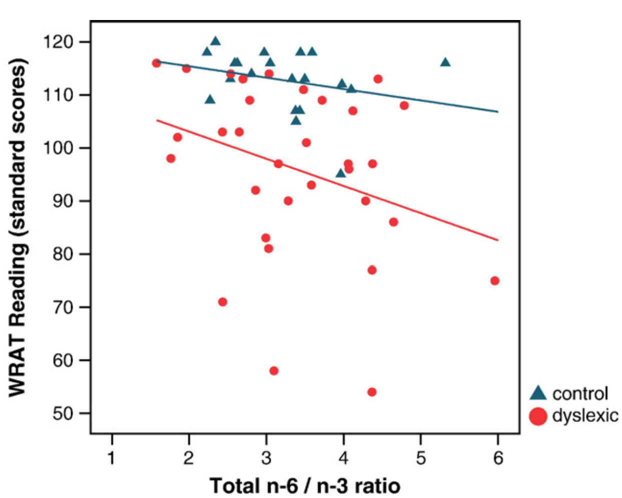

Figure 3 Correlation of reading by n-6/n-3 ratio by group.

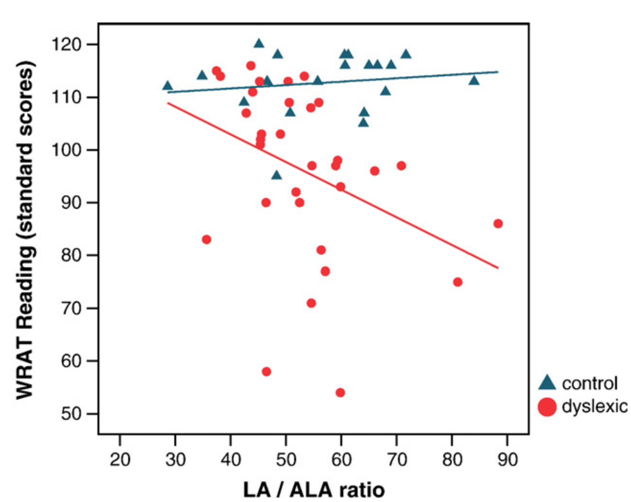

Figure 5 Correlation of reading by LA/ALA ratio by group.

randomised controlled trial of HUFA supplementation in dyslexia is currently underway and is expected to offer further insight about the changes in blood fatty acid composition and the stability of treatment effects on learning. The present findings also suggest that studies of HUFA supplementation in *non-dyslexic* subjects would add useful information about the relationships between reading ability and fatty acid metabolism in general.

Although the extent to which the current findings reflect actual abnormalities of fatty acid metabolism in dyslexia is not yet clear, to our knowledge this is the first study reporting any relationship between blood fatty acids and reading. Our results provide further information about potential risk factors for reading difficulties, and support the hypothesis that lipid metabolism may play a role in learning and behaviour.

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