BIOCHEMICAL PROFILES IN PEOPLE WITH A VISUAL SUB-TYPE OF DYSLEXIA: COMPARISON OF ADULT AND CHILD GROUPS

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Visual Processing Problems and Dyslexia

There is increasing awareness of visual processing problems in people with dyslexia (Booth, Perfetti, MacWhinney, & Hunt, 2000; Helenius & Salmelin, 2002; Skottun, 2000; Stein, 2001; Terepocki, Kruk, & Willows, 2002). One area of investigation has centred upon the proposal by Irlen (1991a) of a specific visual-perceptual dysfunction, which has been called Irlen Syndrome (IS) or visual discomfort (Conlon, Lovegrove, Chekaluk, & Pattison, 1999). The dysfunction is unrelated to skills normally assessed by an optometric examination (Evans, Wilkins, Brown, Busby, Wingfield, Jeanes, & Bald, 1996; Evans, Wilkins, Busby, & Jeanes, 1996; Scott, McWhinnie, Taylor, Stevenson, Irons, Lewis, et al., 2002; Simmers, Gray, & Wilkins, 2001). Symptoms of IS include a blurring and shadowing of letters and words, a doubling, merging or movement of print, eye strain and fatigue, a restricted span of focus and problems focussing for an extended period of time (Irlen, 1991a; Meares, 1980). According to Irlen (1991a) the symptoms can be treated by using individually diagnosed coloured overlays or coloured lenses to filter out the specific wavelengths and frequencies of the white light spectrum to which the person is sensitive.

There have been a number of explanations of the described symptoms, some of which relate to retinal malfunction or retinal hypersensitivity. Grosser and Spafford (1989; 1990) identified extra peripheral cones in the retinas of subjects with Dyslexia, as well as a greater sensitivity to light in peripheral vision. It was hypothesised that this abnormal distribution may lead to letter images in peripheral vision competing with letter images in central vision. Lewine (1999) found that visual evoked responses for subjects with IS showed an organised dipolar pattern with coloured filters reported to reduce symptoms and a more complex field pattern without them. He speculated that people with dyslexia may have a greater distribution of cones in peripheral areas, leading to some linking of cones with rod nerve systems, which may cause letters and words to appear to move. Barbolini (2000) undertook a detailed morphochromatic analysis of the central foveal area of the retina and found significant differences in the digitalised foveal images of people with IS and significant changes in transmittance values for coloured filters reported to reduce distortions. Parker and Henson-Parker (2003) used spectonic data analysis to examine the performance of coloured transparencies reported to reduce visual distortions. They found the transparencies significantly suppressed photon energy to the eye for specific photon bands (light frequency bands), and were able to produce the same effect as the coloured transparencies with mathematically simulated electronic circuits. They hypothesised that depressing photon energy is the underlying physics behind successful coloured transparencies and claim that specific frequencies of light (photon energies) may cause electrochemical abnormalities in the eye's photoreceptors. The uncorrected eye is thus transmitting distorted, high energy electronic signals to the brain when it encounters light frequencies to which it is sensitive, with the analogy used of auditory acoustic feedback experienced when a microphone is placed close to a speaker, causing the sound amplifier circuits to be overdriven. They hypothesise that visual anomalies may thus be corrected by selectively depressing specific frequencies of light (colours) to which the person's visual system is hypersensitive. The authors claimed that optic nerve time series data from the Lewine (1999) study showed a higher power spectrum content for people with IS when not using filters, which is consistent with their theory.

It has also been hypothesised that the identified symptoms could be related to a deficit in the magnocellular visual neurological pathway (Demb, Boynton, Best, & Heeger, 1998), which may cause an overlapping of visual images between consecutive eye fixations when reading (Boden & Brodeur, 1999). Information is transmitted from the eye to the brain by two parallel pathways, the magnocellular (M) pathway and the parvocellular (P) pathway. These two pathways are claimed to have specific roles in reading, with the M pathway guiding eye movements and the P pathway providing detailed information at each focus point or fixation (Williams & Lovegrove, 1992). The movement of eyes from one focus point to the next (saccades) lasts approximately 20 to 40 milliseconds. During this eye movement, visual information does not appear to be processed (Rayner & Pollatsek, 1992). Detail is extracted during the focus or fixation phase which lasts at least 200-300 milliseconds, but could be longer if there are difficulties with word identification (Whiteley & Smith, 2001). Information up to 15 character spaces is extracted during fixation and it is information to the far right of this visual field, which is transmitted by the M pathway, to help guide eye movements to the next word or word cluster important for gaining meaning from text (Whiteley & Smith, 2001). The M pathway is not only claimed to guide eye movements, but may also be involved in suppressing the potential overlap of images between consecutive eye fixations (saccadic suppression; Hussey, 2002). It has been claimed that accumulating evidence suggests deficits in the M pathway may occur in approximately 70% of cases of dyslexia (Whiteley & Smith, 2001).

There have been a number of investigations which support the M deficit hypothesis. Studies have identified a diminished or delayed visual evoked potential for poor readers along the M pathway in response to moving stimuli (Brannan, Solan, Ficarra, & Ong, 1998; Livingstone, Rosen, Drislane, & Galaburda, 1991: Romani, Conte, Callieco, Bergamaschi, Versino, Lanzi et al., 2001). Investigations of poor motion sensitivity (Demb, Boynton, & Heeger, 1998; Slaghuis & Ryan, 1999; Talcott, Hanson, Assoku, & Stein, 2000) have also found a reduced activation of the V5/MT area of the visual cortex, which is sensitive to visual motion

and is dominated by magnocellular input. Cells with large receptive fields receive direct projections from the magnocellular dorsal stream of the posterior parietal cortex, which is important for peripheral vision and the control of saccadic eye movements (Anderson & Mountcastle, 1983). The M deficit hypothesis, however, has been questioned, with claims that the magnocellular system is suppressed, not activated during saccadic eye movements (Scottun, 2000). Chase, Ashourzadeh, Kelly, Monfette, and Kinsey (2003), however, drew different conclusions to Skottun when reviewing the same data, which suggested that the M-pathway could be the primary pathway for text perception at normal contrast levels.

Colour filtering is claimed to influence the functioning ability of the M pathway (Edwards, Hogben, Clark, & Pratt, 1996), with reading performance reported to be better with blue filters (Chase et al., 2003; Iovono, Fletcher, Breitmeyer, & Foorman, 1998). Irlen (2003) also reported that blue and blue-green are the filters most frequently claimed to reduce symptoms of IS. Chase et al. (2003) conducted a number of studies which found that red light suppressed M-cell activation, thus affecting M-pathway activities such as perception of motion, perception of global shape and possibly reading performance. Improvement in M-pathway activities should thus occur with the use of blue filters because longer wavelengths (red) would then be absent (Chase et al., 2003). Coloured filters have also been reported to improve eye movement while reading (Evans, Patel, Wilkins, Lightstone, Eperjesi, Speedwell et al., 1999; Northway, 2003; Robinson & Foreman, 1999a), improve reading performance (Bouldoukian, Wilkins, & Evans, 2002; Robinson & Foreman, 1999b; Scott et al., 2002; Wilkins, Lewis, Smith, Rowland, & Tweedie, 2001) and lead to changes in visual evoked potentials for people with symptoms of IS (Lewine 1999).

Visual Processing Problems and Fatty Acid Metabolism

A number of studies of abnormal fatty acid metabolism in people with dyslexia suggest that visual processing in particular may be affected. Essential fatty acids (EFA) play a primary role in most cell signalling systems in the neurones and are fundamental to neuronal structure, growth, remodelling and function (Horrobin, 1999). The key EFAs need to come from diet (Holman, 1992). If they are not available, they may be replaced by less desirable fatty acids (Horrobin, 1999). There are a variety of factors which may interfere with the fatty acid metabolism, including stress (Brenner, 1981; Horrobin, 1990), and viral infection (De Becker, McGregor, De Smet, & De Meirleir, 2002).

There is evidence of an association between dyslexia and abnormal fatty acid metabolism (MacDonnell, Skinner, Ward, Glen, Glen, McDonald at al., 2000; Rae, Lee, Dixon, Blamire, Thompson, Styles et al., 1998; Richardson, Cox, Sargentoni, & Puri, 1997), in particular for visual symptoms when reading (Richardson, Easton, McDaid, Hall, Montgomery, Clisby, & Puri, 1999; Richardson, Calvin, Clisby, Schoenheimer, Montgomery, Hall et al., 2000; Wilmer & Richardson, 2001). Richardson et al. (1999) found that high signs of EFA deficiency were significantly correlated with visual symptoms when reading and the checklist used to identify visual symptoms had many indicators of IS, including headaches, eye strain, blurring, movement and pulsation of print, light sensitivity and a haloing effect around words (Irlen, 1991a). Richardson et al. (2000) found children with a high level of clinical signs of fatty acid deficiency had significantly poorer reading, and the severity of clinical signs was strongly correlated with visual problems and visual symptoms when reading. Wilmer and Richardson (2001) also identified positive associations between self-reported signs of fatty acid deficiency and a scale assessing typical dyslexic visual and motor symptoms in normal college students. The large size of M neurons and their thick insulating coats of the fatty substance myelin allow them to carry electrical impulses faster than other nerves. Speed is crucial as Livingstone et al. (1991) found the M pathway of dyslexics is slower to send impulses from the retina to the visual cortex (50 milliseconds), which is potentially double the normal transmission time.

There has been some evidence to suggest that supplementation with essential fatty acids may improve retinal and neural function. Highly unsaturated fatty acids, especially Docosahexaenoic acid (DHA) have been found to improve maturation of rod photoreceptor function and visual acuity (Birch, Birch, Hoffman, & Uauy, 1992; Neuringer, Reisbick, & Janowski, 1994), as well as influencing neuronal growth cones (Auestad & Inniss, 2000). The delivery of DHA is also important for the development of mature synapses (Willatts & Forsythe, 2000), with long chain polyunsaturated acids also showing a significant advantage for visual attention and problem solving (Willatts & Forsythe, 2000). A number of studies have found that DHA is important for normal retinal development in humans (Birch, Hoffman, Uauy, Birch, & Prestidge, 1998; Horrocks & Yeo, 1999). Visual evoked potentials in infants in particular may be enhanced by the use of fatty acids (Birch, Garfield, Hoffman, Uauy, & Birch, 2000; Makrides, Neumann, Summer, Pater, & Gibson, 1995), with evidence that the maturation of visual evoked potentials may be faster in infants whose infant formula is supplemented with fatty acids (Faldella, Govoni, Alessandroni, Marchiani, Salvioli, Biagi et al., 1996). Stordy (1995) found the dietary essential fatty acid intake of subjects with poor dark adaptation and symptoms of dyslexia was lower than symptom-free family members, and dietary supplementation normalised dark adaptation within one month. Dark adaptation is known to be a function of retinal rod cells, which require high levels of DHA and Arachidonic acid (AA) for normal structure and

function (Neuringer et al., 1994). These cells also form part of the magnocellular pathway. However, the association between dark adaptation, dyslexia and fatty acid supplementation has been questioned. Greatorex, Drasdo, and Dresser (2000) assessed dark adaptation in young adults with dyslexia and found they had normal dark adaptation curves, similar scotopic threshold responses and similar suprathreshold responses using an electroretinogram. Aguire, Ackland, Maude, and Anderson (1997) claim that while a deficiency in DHA can occur with rod-cone degeneration, their study found that a diet enriched in DHA failed to correct the degeneration.

Biochemical Anomalies and Irlen Syndrome

Robinson and colleagues (Robinson, Roberts, McGregor, Dunstan, & Butt, 1999; Robinson, McGregor, Roberts, Dunstan, & Butt, 2001) have identified a number of biochemical markers for visual processing problems related to IS. The Robinson et al. (1999) study involved 143 adults with Chronic Fatigue Syndrome (CFS) who also had symptoms of IS. Significant anomalies were found in the excretion of a number of amino and organic acids, including leucine, proline, 3-methylhistidine, tyrosine and phenylalanine. These anomalies suggest an alteration in protein and tissue metabolite turnover, which could be indicative of immune system dysfunction and the presence of infection, which in turn may influence the metabolism of fatty acids. The Robinson et al (2001) study involved 61 adults with symptoms of IS and CFS. Significant differences were found in plasma lipid and urinary metabolite levels between people who had low and high symptoms of IS, with cholesterol and lathosterol increasing in the high symptom group. There was also an increase in the long chain polyunsaturated acids CIS 11, 14 and 17-C20:3 and a reduction in the odd-chain saturated fatty acid C17:0 (heptadecanoic acid) between the low and high symptom IS groups. In addition, the dietary derived fatty acid trans-9-C18:1, linked to macular degeneration (Hammond, Fuld, & Snodderley, 1996), was increased in the subjects with high symptoms of IS. The accumulation of trans-9-C18:1 has been shown to induce an alteration in very long chain polyunsaturated fatty acids (Koletzko, 1992).

The evidence and opinion cited above would suggest that biochemical anomalies may play an important role in the aetiology of dyslexia. In particular, fatty acid metabolism has been suggested as a possible causal factor, especially for a visual processing subtype of dyslexia such as IS. However, initial investigations of the relationship between biochemical anomalies and IS (Robinson et al., 1999; Robinson et al., 2001) were confounded by the presence of other disabilities and a study was thus undertaken of both adults and children with symptoms of IS which were not confounded by other medical conditions which may confuse the interpretation of biochemical profiles.

THE PRESENT INVESTIGATION

This study of people who only have symptoms of IS was needed to allow a more detailed analysis of the association between metabolic anomalies and dyslexia. The purpose was to investigate subjects who have symptoms of visual processing problems (IS) but not symptoms of CFS. This study also investigated children as well as adults.

Subjects and Measures

The initial study group involved 51 subjects (mean age=32 years, 1 month) with symptoms of IS, and 54 age- and sex-matched subjects with no symptoms of the syndrome as controls (mean age=29 years, 8 months). The subjects' ages ranged from 10 years to 53 years, with 44% being male. The experimental group were selected from people referred to the Special Education Centre, University of Newcastle for reading and writing problems. The age- and sex-matched control group were recruited primarily from the general public, but also from relatives of subjects with IS.

All subjects were screened for symptoms of IS using the Scotopic Sensitivity Syndrome Screening Manual (Irlen, 1991b). Validity studies of the Irlen Manual by Robinson, Hopkins, and Davies (1995) and Tyrrell, Holland, Dennis, and Wilkins (1995) have found significant differences on scores in all sections between reading disabled and normally achieving students. Gray (1999) found significant relationships between scores on the manual and standardised measures of reading achievement, spelling achievement and visual processing. A high test-retest reliability for identification of symptoms and colour choice has also been identified by Jeanes, Busby, Martin, Lewis, Stevenson, Pointon et al. (1997), Robinson and Foreman (1999b), Wilkins (1997), and Wilkins et al. (2001). Subjects from the initial sample who reported a history of major organic or psychiatric conditions, including anxiety, depression or Attention Deficit Hyperactivity Disorder (ADHD) and Attention Deficit Disorder (ADD), were excluded from the analysis.

Serum Lipid and Urine Specimens and Gas Chromatography/Mass Spectometry (GC-MS) Identification

The study subjects provided a first of the morning urine sample for analysis using gas chromatography and mass spectrometry (GC-MS) (McGregor, Dunstan, Zerbes, Butt, Roberts, & Klineberg, 1996a). All subjects had completed a collaborative pain research uni (CPRU) symptom questionnaire completed on the day of their biochemical test. Ten ml of whole blood was also collected from the study subjects by venipuncture into a lithium heparin vacu-tainer (Becton Dickinson) and processed using a Hewlett Packard 5890 series II gas chromatograph and series 5971A Mass Selective Detector (McGregor, Dunstan, Zerbes, Butt, Roberts, & Klineberg, 1996b). The subjects had fasted for 12 hours prior to the blood collection, and were asked to list the drugs and naturopathic remedies they had taken, as well as dietary changes they had made during the preceding four weeks.

Statistical Analysis

Percentage composition lipid and urine data were arcsine transformed before analysis to improve normality. Subject characteristics were assessed using Chi-square analysis. Metabolites were compared using Student's t-test and discriminant function analysis. These data were processed using Access 2000 TM (Microsoft, Redmond, WA, USA) and Statistica TM (Ver. 6, Statsoft, Tulsa, OK, USA).

Results

There were significant differences between experimental and control groups in a number of amino acids and serum lipids as outlined in Tables 1 to 4.

Table 1
Significant differences in the concentration and percentage abundance of amino acids between IS and Control groups for Adults and Juveniles

Concentration

Juveniles (IS:n=13; Ctl:n=18)		**Adults** (IS:n=12; Ctl:n=19)	
Amino Acid	**t-test p value**	**Amino Acid**	**t-test p value**
Increased		No differences for amino acid concentration	
Serine	<.02		
Alanine	<.03		
UM17	<.04		

Student's t-test performed on standardised log transformed data

Percentage Abundance

Juveniles (IS:n=13; Ctl:n=18)		**Adults** (IS:n=12; Ctl:n=19)	
Amino Acid	**t-test p value**	**Amino Acid**	**t-test p value**
Increased		Decreased	
UM17	<.008	Aconitic Acid	<.05
Alanine	<.02		

Student's t-test performed on arcsine transformed percentage abundance data

A number of amino acid excretion anomalies were found for the IS cohort in comparison with the control group. The non-essential amino acids serine and alanine were both excreted in higher amounts for the IS group. Alanine is involved in numerous metabolic processes such as nitrogen metabolism, transamination and gluconeogenesis (McGregor, De Becker, & De Meirleir, 2002). Serine acts as a precursor of the amino acid ethanolamine, with both ethanolamine and serine forming integral parts of the cell membrane phospholipids, phoshatidylserine and phosphatidylethanolamine. Serine is also a precursor of glycine, which functions as a neurotransmitter and is involved in the formation of bile salts from

cholesterol. Alterations in serine excretion are of particular interest due to the known link between IS and CFS (Robinson et al., 2001). A number of CFS patients have claimed that following supplementation with serine they have been able to read again. The amino acid UM17 has also been detected in the urine of people with CFS.

Table 2
Significant correlations between urinary metabolite concentration and core IS symptom severity and symptom improvement within the Adult and Juvenile IS study groups

IS Symptom	Metabolite	Spearman R	P value
Adults			
Print distortion (severity)	phenylacetic acid	-0.66	<0.02
Print distortion (improvement)	lysine	0.60	<0.04
	3-methylhistidine	0.58	<0.05
Photophobia (severity)	UM27	0.77	<0.004
	lysine	0.72	<0.009
	phenylalanine	0.63	<0.03
	UM28	0.61	<0.05
Photophobia (improvement)	UM27	0.74	<0.006
	1-methylhistidine	0.61	<0.04
Juveniles			
Print distortion (severity)	serine	-0.63	<0.03
	threonine	-0.58	<0.04
Reading assessment	serine	-0.58	<0.04

Statistical method = Spearman rank order correlation analysis.

Table 3
Significant correlations between urinary metabolite percentage abundance and core IS symptom severity and symptom improvement within the Adult and Juvenile IS study groups

IS Symptom	Metabolite	Spearman R	P value
Adults			
Print distortion (severity)	UM27	0.75	<0.005
	3-methylhistidine	0.66	<0.02
	lysine	0.64	<0.03
	phenylacetic acid	-0.82	<0.002
	glycine	-0.67	<0.02
	succinic acid	-0.67	<0.02
	glutamic acid	-0.60	<0.05
Print distortion (improvement)	lysine	0.67	<0.02
	3-methylhistidine	0.65	<0.03
	CFSUM1	0.62	<0.04
Reading difficulties (severity)	UM27	0.71	<0.01
	Valine	-0.63	<0.03

Reading difficulties (improvement)	Phenylacetic acid	-0.65	<0.03
	serine	-0.59	<0.05
Juveniles			
Print distortion (severity)	1-methylhistidine	0.64	<0.02
	3-methylhistidine	0.60	<0.03
Print distortion (improvement)	1-methylhistidine	0.64	<0.02
	phenylalanine	0.56	<0.05
Reading difficulties (severity)	1-methylhistidine	0.59	<0.04
	3-methylhistidine	0.59	<0.04

Statistical method = Spearman rank order correlation analysis.

Again, a number of differences were found in the excreted or urinary concentration of amino acids in relation to symptom severity and improvement for the IS group. The function of the amino acid serine was discussed above. The urinary metabolite phenylalanine is increased in severe infection (Wannemacher, Dinterman, Pekarek, Bartelloni, & Beisel, 1975) and indicators of immune system activation and the presence of infection were identified in people with symptoms of IS in studies by Robinson and colleagues (Robinson et al., 1999, 2001). The higher incidence of ulceration in the IS group in this study (Table 7) could be an indicator of infection. While mouth ulcers have numerous causes, they can be indicators of viral reactivation (McGregor et al., 2002). Aldred, Moore, Fitzgerald, and Waring (2003) also found significant differences in levels of phenylalanine, alanine and glutamate in people with symptoms of autism spectrum disorder when compared to controls. Knivsberg, Reichelt, and Nødland (2001) and Richardson and Ross (2000) suggest that biochemical anomalies may play a common role in both dyslexia and autism. Bell, Sargent, Tolcher, and Dick (2000) reported a single case study of a person with autism who had an instability of HUFA, which was consistent with anomalies found in dyslexia (MacDonnell et al., 2000).

The urinary metabolites 3-methylhistidine and 1-methylhistidine are both found in the actin molecule, with 3-methylhistidine being an indicator of immune system activation and the presence of infection (Wannermacher et al., 1975). In particular, 3-methylhistidine is considered to be a reliable indicator of muscle fibrillar catabolism, which involves using amino acids from other areas of the body such as muscles to fight infection. During such a catabolic event the proteins found in the muscle are broken down to yield their constituent amino acids such as 3-methylhistidine which, in turn, results in an increase in excretion of 3-methylhistidine. A significant difference in 3-methylhistidine was found in subjects with CFS who have symptoms of IS in previous studies by Robinson and colleagues (Robinson et al., 1999, 2001). Increases in post viral tissue turnover can result in a dysregulation of fatty acid metabolism (Horrobin, Glen, & Hudson, 1995), and abnormal fatty acid metabolism has been associated with visual symptoms and visual processing problems in dyslexia (Richardson et al., 2000; Stordy, 1995). There has also been associations between fatty acids and retinal function (Birch et al., 1998; Neuringer et al., 1994), as well as between fatty acids and the function of the M pathway (Rae et al., 1998; Taylor & Richardson, 2000).

Glycine has been found to be elevated in people with migraine and tension headache (Alam, Coombes, Waring, Williams, & Steventon, 1998) and people with IS report a high incidence of headaches and migraine (Evans, Patel, & Wilkins, 2002; Irlen, 1991a), as well as a reduction in these symptoms when using coloured filters (Chronicle & Wilkins, 1991; Evans et al., 2002; Good, Taylor, & Mortimer, 1991). Significant differences were found in succinic acid and UM28 for subjects with CFS who have symptoms of IS by Robinson et al. (1999).

Table 4
Significant differences in the relative abundance of plasma lipids for Adult and Juvenile Control and IS Groups

Lipid component	Control (mean±SEM)	IS (mean±SEM)	t-test P value
	Adults		
% Heptadecanoic acid	0.21±0.01	0.22±0.01	NS
Total cholesterol	4.29±0.15	4.46±0.24	NS
	Juveniles		
Heptadecanoic acid (%)	0.20±0.01	0.25±0.02	<0.03
Total cholesterol	3.90±0.15	3.42±0.15	<0.05

Note: Student's t-test performed on log-transformed data and arcsine-transformed percentage abundance data.

The significant difference in heptadecanoic acid between IS and controls for juvenile groups is important, as odd chain fatty acids are in the coat of certain viruses and may impair proper cellular chemistry (Shoemaker, 2001a). These fatty acids are not produced by humans and may be influenced by diet. A similar difference in heptadecanoic acid was found by Robinson et al. (2001). Essential fatty acids may compete with saturated and monosaturated fatty acids for incorporation into phospholipids (Horrobin, 1999). Horrobin (1999) has further suggested that when essential fatty acids in brain phospholipids are lowered, an increased in saturated fatty acids may worsen conditions such as schizophrenia. It could thus be that the increased incorporation of the saturated fatty acid, heptadecanoic acid, could lead to alterations in compositions of cell membrane lipids and have implications for altered membrane function and neurotransmission.

The difference in heptadecanoic acid between the control and IS groups for juveniles may also point to the presence of chronic viral or bacterial infection. Williams, Lew, Davidorf, Pelok, Singley, and Wollinski (1994) found odd-chain fatty acids, which do not usually occur in human cells, in human retinal pigment infected with the rubella virus. The changes in cholesterol level, in this study, as found by Robinson et al., 2001, may also occur in response to viral and bacterial infection (Pfeffer, Kwok, Landsberger, & Tamm, 1985), with plasma cholesterol levels likely to deplete the supply of essential fatty acids (Hibbeln & Salem, 1996b, Sardesai, 1992). There were also anecdotal reports from subjects in the Robinson et al. (2001) study of visual improvement following the use of amino acid supplements and/or antibiotic treatment for co-morbid bacterial problems.

While significant differences were not found between control and IS groups for EFAs (possibly due to low subject numbers), there were lower mean levels in most n-3 and n-6 EFAs for the juvenile IS group, as shown in Table 5.

Table 5
Univariate analysis of the percentage abundance of plasma lipids for juvenile control and IS groups

Lipid Component	Control	IS	t-test p value
n-6			
Linoleic acid	13.63 ± 0.31	13.13 ± 0.63	NS
DGLA	0.65 ± 0.61	0.53 ± 0.06	NS
Arachidonic acid	1.03 ± 0.23	0.78 ± 0.22	NS
n-3			
Eicosapentaenoic acid	0.09 ± 0.03	0.06 ± 0.02	NS
Docosahexaenoic acid	0.13 ± 0.05	0.10 ± 0.03	NS

The capacity of biochemical profiling to identify both children and adults with symptoms of IS was calculated by discriminant function analysis, as shown in Table 6.

Table 6
Forward Stepwise discriminant function analysis of differences in the plasma lipid profiles: Comparison between Adult and Juvenile Control and IS groups

Forward Stepwise Discriminant Function Analysis

Plasma Lipid Percentage Abundance
Model statistics
Wilks' Lambda = 0.18, F(39,131) = 2.67, p<0.0000

Classification accuracy (%)

Adult Control	Adult IS	Juvenile Control	Juvenile IS	Total
61.11	83.33	70.59	76.92	71.67

Values calculated using arcsine transformed percentage data.

A Wilks' Lambda value of 0 is perfect discrimination and a value of 1 is no discrimination. Based on the lipid profiles, the Control and IS subjects were correctly predicted 72% of the time. The results of forward stepwise discriminant function analysis identified the primary metabolite in the discrimination between IS and Control groups as the odd chain fatty acid heptadecanoic acid.

The high degree of accuracy in identifying both adults and children through biochemical profiling suggests that this method offers promise as a means of early identification and as a process for establishing the validity of the syndrome. Identification of biochemical "markers" for the specific visual processing symptoms of IS could allow much earlier identification and also contribute to a more accurate identification. Early diagnosis is important for the large numbers of the school population with dyslexia, as lack of early reading success can lead to discouragement, a passive learning style and further failure (Wong, 1986). It has been claimed that many children with a reading disability are not diagnosed until they are about 9 years old (McLesky, 1992). By this age, they may have experienced significant and prolonged failure and are unlikely to bridge and academic gap between them and their peers (Foorman, Francis, Fletcher, Schatschneider, & Mehta, 1998).

The significant differences between experimental and control groups in reported prevalence of medical conditions, as well as in emotional, cognitive and possible neurological symptoms is identified in Table 7.

Table 7
Sensitivity and specificity of response to a general health questionnaire

Symptom	Sensitivity (%)	Specificity (%)	P value
General			
photophobia	68.0	83.8	<0.0002
aphthous ulceration	32.0	100	<0.0004
allergies	44.0	89.2	<0.008
Neurocognitive			
memory disturbance	80.0	67.6	<0.0003
forgetfulness	84.0	62.2	<0.004
mental confusion	64.0	73.0	<0.004
trouble concentrating	80.0	51.4	<0.03
Mood Change			
unpleasant thoughts	60.0	73.0	<0.01
nervous when alone	40.0	86.5	<0.04

Statistical test: Chi-square test and Fisher exact probability test

The significant difference in photophobia is an important symptom indicator of IS (Irlen, 1991a; Tyrrell et al., 1995; Lightstone, Lightstone, & Wilkins, 1999). The significant difference in trouble concentrating and mental confusion have also been identified as symptom indicators of IS (Irlen, 1991a; Irlen & Robinson, 1996; Whiting, Robinson, & Parrot, 1994). The higher incidence of mouth ulcers and allergies could suggest an immune system dysfunction, and immunological problems have been suggested as a cause of dyslexia (Galaburda, 1997; Knivsberg, 1997). There were also indications of immune system dysfunction as indicated by suggestions of recurring infection in studies by Robinson and colleagues (Robinson et al., 1999, 2001). The mood change variables might be expected for any person who has experienced reading difficulties and lacks confidence (Wong, 1986), however, they might be more prevalent in the IS group, as Cotton and Evans (1990) found that children with IS are more likely to be neurotic, anxious and have a lowered self-concept than other children with a reading disability. These mood changes may be related to alterations in cholesterol levels, as behavioural changes have been noted in patients whose high cholesterol levels have been lowered through drug and dietary intervention (Hibbeln & Salem, 1996a). Cholesterol lowering therapies have been linked to depression and aggression, with Kaplan, Shively, Fontenot, Morgan, Howell, Manuck et al. (1994) suggesting these behaviours are mediated by changes in the activity of the neurotransmitter serotonin. Hibbeln, Umhau, George, Shoaf, Linnoila, and Salem (2000) suggested the drug and dietary treatments might have lowered both plasma cholesterol and the tissue concentrations of highly unsaturated fatty acids, which play a crucial role in cell membrane function and neurotransmission.

DISCUSSION

The differences in lipid and urine biochemistry between experimental and control groups supports the hypothesis of an association between metabolic anomalies and various forms of disability, including problems with neural function and visual processing problems (Richardson & Ross, 2000). However, no significant alterations were found in essential fatty acid homeostasis, although there were lower mean levels in most n-3 and n-6 essential fatty acids for the juvenile IS experimental group in this study. It is unclear whether subjects in the studies by Richardson and colleagues were free of comorbid pathologies such as attention or hyperactivity disorders in which serum and plasma essential fatty acid levels may be altered (Mitchell, Aman, Turbott, & Manku, 1987; Burgess, Stevens, Shang, & Peck, 2000; Stevens, Zentall, & Deck, 1995). Richardson et al. (2000) state that in studies of fatty acid metabolism, the features of both dyslexia and ADHD should be assessed due to the high level of comorbidity of the two conditions. In the present study, subjects with a previous diagnosis of ADHD were excluded to provide a high level of homogeneity within the subject group.

While the evaluation of the relative percentage abundance data revealed that there were no qualitative differences in essential fatty acid profiles, they did reveal differences in total plasma cholesterol for the juvenile group. Total plasma cholesterol was significantly decreased ($P<0.05$) for the IS group of juveniles compared with controls (Table 4) with 85% of the Irlen Syndrome subjects having cholesterol levels below the control group mean. It is thought that the highly myelinated magnocells, believed to be deficient in dyslexia, may be prone to cellular malnutrition during disease due to their relatively high metabolic requirements. The magnocellular pathway is selectively compromised in the early stages of a number of diseases (Lehmkuhle, 1993). In the human brain cholesterol is a significant component, with most of this cholesterol being found within myelin (Snipes & Suter, 1997).

Changes in the levels of odd-chain fatty acids, as found in this study (Table 4), can occur in some disorders of fatty acid metabolism. In humans, increases in the odd-chain fatty acid composition of phospholipids and cholesterol ester have been documented (Mock, Johnson, & Holman, 1988). Richardson and Puri (1999) identified indicators of anomalies in brain phospholipid metabolism which, they claim, are in agreement with existence of essential fatty acid deficiency in dyslexia. Incorporation of odd-chain fatty acids, such as C17:0, would also lead to alterations in the composition of cell membrane lipids and could have implications for altered membrane function and neurotransmission, although plasma cholesterol levels are not necessarily associated with brain cholesterol levels, as brain cholesterol does not cross the blood-brain barrier.

The difference in C17:0 and changes in total cholesterol levels may also point to the presence of a chronic viral or bacterial infection. A decrease in total cholesterol levels within human serum has been demonstrated in response to human leucocyte interferon (Dixon, Borden, Keim, Anderson, Spennetta, Tormey, & Shrago, 1984), interferon being produced in response to viral infection. In a study of cultured human retinal pigment epithelium, which was persistently infected with the rubella virus, there was an indication of the presence in cell membranes of odd-chain fatty acids not usually occurring in human cells and increased levels of saturated fatty acids. Williams et al. (1994) concluded that persistent infection with the rubella virus resulting in altered fatty acid components of membrane phospholipids and increased saturated fatty acid abundance would have implications for membrane fluidity and cellular function.

Overlapping Diagnostic Categories?

These preliminary data represent only the beginning to understanding a wide range of disabilities, which at the moment are subsumed under broad and overlapping diagnostic categories such as dyslexia, specific learning disabilities, ADHD, dyspraxia and CFS. The extent of overlap between these categories is so extensive that the category used for any individual may in some cases be dependent upon the background of the attending professional. Comings (1996) and McCrone (1998), for example, suggest that a variety of biochemical anomalies are likely to be implicated in learning and behaviour problems, and various combinations of these anomalies may cause a variety of overlapping disabilities. Hardman and Morton (1991) found that 98% of subjects who were chemically dependent (referred to a drug and alcohol rehabilitation centre) also had symptoms of dyslexia, and 89% had symptoms of ADD. Hyperactive children have also been found to have significantly lower serum and plasma levels of essential fatty acids (Mitchell et al., 1987; Stevens et al., 1995). Phospholipid abnormalities have also been identified in people with dyslexia similar to those identified in people with schizophrenia (Horrobin, Glen, & Hudson, 1995; MacDonnell at al., 2000). Richardson and Ross (2000) hypothesise that abnormalities of fatty acid and membrane phospholipid metabolism may be a factor in a wide range of disorders, including attention deficit/hyperactivity disorder, dyslexia, dyspraxia and autistic spectrum disorder, which they feel could explain the high degree of co-morbidity between these conditions.

The analysis of biochemical anomalies could be particularly important in the development of more valid diagnostic categories. It offers the hope that in time we may be able to develop a biochemical profile of each individual. This profile could allow us to effectively identify which individuals are likely to have specific difficulties in certain learning/social situations, and to provide appropriate treatment. Biochemical analysis may be particularly important for identifying those symptoms which are the cause of the disorder as distinct from those which are the result of the disorder (Pennington, 1989). It is important that treatment strategies are based on causes rather than on overt behavioural symptoms or responses. With current diagnostic categories, the behavioural symptoms for "non-visible disabilities", such as IS, ADD or CFS, are predominantly treated as the cause, with students being told to "try harder" or "concentrate more", which is likely to have a minimal effect if they cannot concentrate (ADHD), feel fatigued (CFS), or have eye strain and a progressive distortion of print while reading (IS). Biochemical analysis may also help to highlight the fact that overlapping disabilities may mean multiple treatments are required (Hardman & Morton, 1991). Identification and treatment of the “highly visible” disability, ADHD, for example, might mean that the possibility of other disabilities and treatments is not considered. It is also likely that treatments might cross traditional diagnostic boundaries, such as the possible use of diet to overcome problems with fatty acid metabolism for dyslexia, ADHD and autism. The development of more effective diagnostic categories through biochemical analysis could also allow a more rational evaluation of the most effective treatment strategies. The broad diagnostic categories currently used are likely to result in a variety of disabilities, or sub-groups of a disability, being present in any one study population (Farmer & Klein, 1995; Torgesen, 1998). As a consequence, when researchers attempt to compare findings, they are frequently conflicting, due to patient group heterogeneity.

Possible Immune System Deficiencies?

Stein (2000) and Galaburda (1997) cite evidence that dyslexics and their families have a greater than normal incidence of autoimmune disorders, while Knivsberg’s (1997) analysis of urine samples found more abnormalities suggestive of immune system dysfunction in the urine patterns of dyslexics. Hardman and Morton (1991) found 82% of a sample of subjects with symptoms of dyslexia and ADD had significant evidence of allergies or immunological problems, as well as a pattern of diseases associated with immune deficiencies and altered biochemistry. A number of other authors have also reported an association between immune disorders and dyslexia (Armstrong, Seidel, & Swales, 1993; Hugdahl, 1995; Wood & Cooper, 1992). In humans, fatty acid deficiency increases susceptibility to infection (Sardesai, 1992), with serum fatty acid levels falling in several acute viral infections and playing an important role in immunity (De Becker et al., 2002). Animals deficient in essential fatty acids have also shown an altered immune response (Hwang, 1989).

Further evidence of the association between learning disabilities/visual processing problems and immune system dysfunction comes from studies of the effects of exposure to neurotoxins on visual contrast sensitivity. Contrast sensitivity is considered to be an indication of neurological function between the retina and the cortex (Shoemaker & Hudnell, 2001; Turf, Ingsriswang, Turf, Ball, Stutts, Taylor et al., 1999). Spatial vision is mediated by the parvocellular and magnocellular pathways, which have been found to be vulnerable to neurotoxins (Pasternak, Flood, Eskin, & Merigan, 1985).

A number of studies of watermen and recreational fishermen exposed to Pfiesteria infection (which releases toxins that kill fish) have found a significant reduction in visual contrast sensitivity in the mid-range frequencies (Hudnell, House, Schmid, Koltai, Stopford, Wilkins et al., 2001; Shoemaker, 2001a; Shoemaker

& Hudnell, 2001; Swinker, Koltai, Wilkins, Hudnell, Hall, Darcy et al., 2001; Turf et al., 1999). Hudnell et al. (2001) found the magnitude of deficit increased with increasing hours of contact with fish kills and the deficit was reduced with clinical trials of a medication (cholestramyne), suggesting a neural, not an optical physiological basis for improvement. Cholestramyne is a cholesterol lowering drug and Shoemaker (2001b) claims the neurotoxins are fat-soluble and are removed from the bile and prevented from being re-absorbed within the gastrointestinal tract by being bound by Cholestramyne.

Shoemaker (2001b) concluded that the identified symptoms, including problems with concentration, confusion and short-term memory, overlap with symptoms commonly observed in children diagnosed with learning difficulties. Glasgow, Burkholder, Schmechel, Tester, and Rublee (1995), and Grattan, Oldach, Perl, Lowitt, Matuszak, Dickson et al. (1998) found that cases of exposure to Pfiesteria had difficulties in learning new words, reading, spatial orientation, visual speed and accuracy, headaches, blurring, and sensitivity to light, all of which are common symptoms of IS. Both Glasgow et al. (1995) and Shoemaker and Hudnell (2001) further claim that the symptoms seen in some cases suggest the immunological system may be compromised. These symptoms included asthma, chronic colds, respiratory infections and low T-cell counts. There is also evidence that one of the effects of the common cold or influenza may be to impair visual processing performance (Smith, Tyrrell, Coyle, & Willman, 1987; Smith, Tyrrell, al-Nakib, Coyle, Donovan, Higgins, & Willman, 1988; Smith, Tyrrell, Coyle, Higgins, & Willman, 1990; Smith, Tyrrell, Barrow, Higgins, Bull, Trickett, & Wilkins, 1992). Smith et al. (1987, 1988) found that cold infections significantly reduced performance on visual tracking and motor coordination tasks and influenza significantly effected visual scanning, which involved searching lines of letters for the presence of targeted letters. In a further study, Smith et al. (1990) found infection with the cold virus resulted in a slower reaction time to tasks involving letter identification (with distractors) and identification of sequences of numbers. Smith et al. (1992) further assessed the effects of the same cold virus and found volunteers affected were more sensitive to and reported more illusions on a pattern sensitivity test. This pattern sensitivity test has been reported to cause similar difficulties for people with IS (Evans et al., 2002; Wilkins, 1991).

The reduction in contrast sensitivity in mid-range frequencies in people exposed to estuarine infection has also been identified in people chronically exposed to neurotoxic agents, such as solvents and in urban areas of high pollution (Frenette, Mergler, & Bowler, 1991; Hudnell, Otto, & House, 1996; Mergler, 1995; Schreiber, Hudnell, & Parker, 1998). The exposure has been found to affect a range of skills related to learning disabilities, including attention, executive function, visual spatial ability, visual evoked potential and hand-eye coordination tasks (Dahl, White, Weike, Sorensen, Letz, Hudnell et al., 1996; Feldman, 1999; Swinker et al., 2001).

Roberts, Dunstan, Robinson, Cosford, Bull, McGregor, Ellis, and Sparkes (2002) claim that the changes in amino acids and fatty acids may be the consequence of chronic unresolved infection. The body chemistry changes required to fight infection can include using amino acids from other areas of the body, such as muscles, which are a major reservoir of amino acids. This action is called muscle fibrillar catabolism, and unresolved infection may lead to chronic activation of the immune system and in a chronic catabolic state. This continual activation of the immune system may thus eventually lead to malnutrition in terms of amino acids and essential fatty acids.

Dietary Intervention as a Treatment Option?

The identification of a possible dysregulated metabolism in people with dyslexia raises the question of dietary manipulation and food supplementation. Fatty acid metabolism has been implicated as a potential causative mechanism for dyslexia and if the conversion of EFAs to Highly Unsaturated Fatty Acids (HUFA) is impaired, the only way for the brain to obtain the EFA it requires is through diet (Horrobin, 1999). Holman, Johnson, and Hatch (1982) reported a case of linolenic acid deficiency in a child with neurological symptoms including blurred vision, which disappeared with a linolenic acid-rich diet. Visual loss in infant rhesus monkeys deprived of linolenic acid has also been demonstrated (Neuringer, Connor, van Petten, & Barstad, 1984), with other studies of linolenic acid status in animals reporting poor performance on visual discrimination tasks (Lamptey & Walker, 1976; Yamamoto, Saitoh, Moriuchi, Nomura, & Okuyama, 1987). Richardson, Taylor, Montgomery, Calum, Schoenheimer, Hall et al. (2001) also reported significant improvements in reading for children with dyslexia who took a HUFA supplement. The supplementation had a greater effect for children scoring high at baseline in visual symptoms while reading and these visual symptoms include many indicators of IS (blurring, movement and pulsation of print, sensitivity to light and headaches/eye strain while reading). Visual function in infants would also appear to be enhanced by fatty acid supplementation (Birch et al., 1998; Faldella et al., 1996; Uauy, Mena, & Valenzuela, 1999; Willats & Forsythe, 2000).

Dietary intervention has also been shown to have a positive effect for people with ADHD and there is clinical overlap between ADHD and dyslexia (Pisecco, Baker, Silva, & Brooke, 2001). Richardson and Ross (2000) claim this overlap is 30% to 50%, with suggestions that it is even higher for the attention deficit

form rather than the hyperactive form of ADHD (Hynd, Lorys, Semrud-Clikeman, Nieves, Huettner, & Lahey, 1991). Children with ADHD have been found to have significantly lower proportions of key essential fatty acids than did controls (Burgess, Stevens, Zhang, & Peck, 2000; Mitchell et al., 1987; Stevens, Zentall, Abate, Watkins, Lipp, & Burgess, 1995, Stevens, Zentall, Abate, Kuczek, & Burgess, 1996). In one study, children with ADHD were found to be breastfed as infants less often than controls (Stevens et al., 1995) and breast milk contains adequate EFAs. A more recent double-blind crossover study (Richardson & Puri, 2002) found a significant reduction in attentional difficulties and general behaviour problems with a HUFA supplementation. A wide range of other placebo controlled and blinded studies (Boris & Mandel, 1994; Carter, Urbanowicz, Hemsley, Mantilla, Strobel, Graham, & Taylor, 1993; Egger, Carter, Graham, Gumley, & Soothill, 1985; Egger, Stoller, & McEwen, 1993), as well as a study of peptide abnormalities (Knivsberg, Nødland, Reichelt, & Fosse, 2000) have found improvements in behaviour following diet. In particular, Uhlig, Merkenschlager, Brandmaier, and Egger (1997) found a significant increase in beta brain electrical activity for children with ADHD following the ingestion of previously identified provoking foods. Chiang, Misner, and Kemperman (1999) claim that treatment with EFAs would facilitate the connection of the retinoid receptor pathways critical for vision, sensory perception and attention. Mitchell et al. (1987), however, claim that it is unlikely a simple deficiency in EFA is the problem, or there would be more signs of ADD in other disease states where one fatty acid (dihomogamma-linolenic acid) is low, such as cystic fibrosis.

There have also been a number of studies which found benefits following treatment with omega-3 fatty acids for the management of schizophrenia (Peet & Horrobin, 2000; Richardson & Ross, 2000; Shah, Ramchand, & Peet, 2000), with Horrobin (1999) postulating that in individuals who develop schizophrenia, there is an accelerated loss of unsaturated fatty acids. Richardson and Puri (1999) also report a single case study of a subject with both schizophrenia and dyslexia, in which there was a reduction in visual symptoms when reading and improvements in reading, spelling and visual motion sensitivity when provided EFA treatment. The measure of impaired motion sensitivity used in the Richardson and Puri study has been associated with magnocellular function and dyslexia (Stein, 2001).

An immediate challenge would be to identify whether changes in diet lead to changes in identified biochemical profiles and to changes in visual symptoms. It would also be interesting to explore whether dietary intervention leads to changes in neural responses, as identified by Uhlig et al. (1997) in relation to dietary changes for children with ADHD. It should be noted, however, that while supplementation based on biochemical anomalies would seem to be an efficient approach to testing a causative relationship, the degree to which supplementation will be effective will depend on the original cause of the anomaly. There is also a possibility that the body may be able to adapt to dietary deficiencies. Anderson, Benolken, Dudley, Landis, and Wheeler (1974) found that the retinas of rats conserve their omega-3 and omega-6 polyunsaturates during essential fatty acid deficiency, with the renewal of photoreceptor membranes ceasing.

CONCLUSION

There is growing evidence of a biochemical basis for a variety of learning and behavioural problems, including a visual processing sub-type of dyslexia (IS), which was the subject of this paper. The results obtained support the possibility of a role for subtle alterations in cell membrane structure, function and, hence, neurotransmission. There are, however, many questions which remain unanswered, and a great deal of further research is clearly needed if we are to determine the place of biochemical anomalies as a method of early identification and as a possible underlying causal mechanism. Learning to read involves many cognitive processes and a breakdown in any of these processes may affect ability to read. Identifying the place of biochemical anomalies in this complex skill is made harder because of the likely interaction between biochemical status and environmental influences. It has been further suggested that biochemical anomalies and/or neural malfunction may operate in a reciprocal causation cycle (Farmer & Klein, 1995; Stein & Talcott, 1999), with changes in brain chemistry leading to alterations in neural functioning, which could lead to further changes in brain chemistry. It is likely that medication aimed at a specific neurotransmitter may inevitably alter others, especially as disabilities such as dyslexia and ADHD, are a diverse collection of disorders and any single drug could have different outcomes for different people. Holman et al. (1982) found that dietary intakes of one essential fatty acid may suppress the metabolism of another. The real world rarely involves simple linear explanations of a single link between cause and effect. Usually systems are complex with many variables that may not be understood or even recognised.

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