BIOCHEMICAL ANOMALIES IN PEOPLE WITH IRLEN SYNDROME

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The Nature of Irlen Syndrome and Possible Causal Mechanisms

In the last decade, there has been increasing awareness of visual processing problems in people with dyslexia (Chase, Ashourzadeh, Kelly, Monfette, & Kinsey, 2003; Helenius & Salmelin, 2002; Terepocki, Kruk, & Willows, 2002; Watson, Kidd, Horner, Connell, Lowther, Eddins et al., 2003). 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). This dysfunction is not related to regular optometric problems, although binocular and accommodative anomalies may occur in conjunction with IS (Evans, Patel, Wilkins, Lightstone, Eperjesi, Speedwell et al., 1999; 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). These binocular and accommodative anomalies are not considered to be the underlying mechanism for the benefit of coloured filters (Scott et al., 2002; Simmers et al., 2001). Symptoms of IS may include a blurring and shadowing of letters and words, a doubling, merging or movement of print, eye strain and fatigue while reading, 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 wavelengths and frequencies of the white light spectrum to which the person is sensitive, with the optimal colour being very specific to each individual (Wilkins, Evans, Brown, Busby, Wingfield, Jeanes et al., 1994).

One explanation of the symptoms described by Irlen suggests a retinal abnormality or hypersensitivity. Lewine (1999) found that visual evoked responses for subjects with IS showed an organised dipolar pattern when using 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 of the retina, 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. Significant changes in the amplitude and phase of visual evoked potentials have also been reported in another study of tinted lens wearers (Riddell, Wilkins, Zemori, Gordon, & Hainline, 1998). 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 light energy to the eye for specific light frequency bands, and hypothesised that depressing light energy is the underlying physics behind successful coloured transparencies. They further claim that specific frequencies of light (colours) may cause electrochemical abnormalities in the eye's photoreceptors, with distorted, high energy electronic signals being transmitted to the brain when it encounters light frequencies to which it is sensitive. They hypothesise that visual anomalies may thus be corrected by selectively depressing the 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. The concept of a hypersensitive visual system has also been proposed by Wilkins and colleagues (Wilkins, 2003; Wilkins, Huang, & Chao, 2004). It was hypothesised that people with Irlen Syndrome may have a hyperexcitable visual cortex and that comfortable colours might reduce this strong excitation and the accompanying illusory effects.

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 (saccadic suppression; Hussey, 2002; 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 the fixation phase and it is information to the far right of this visual field, which is transmitted by the M pathway, which helps 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 when reading (saccadic suppression). 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

MT area of the visual cortex for poor readers, with reduction in MT activity being correlated with reading achievement (Demb, Boynton, & Heeger, 1997). The MT area is sensitive to visual motion and is dominated by magnocellular input. 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), with estimates of incidence of IS in the general population ranging from 12% to 20% (Evans et al., 1999; Irlen, 1997; Jeanes, Busby, Martin, Lewis, Stevenson, Pointon et al., 1997; Robinson, Hopkins, & Davies, 1995; Scott et al., 2002).

Colour filtering is claimed to influence the functioning ability of the M pathway (Edwards, Hogben, Clark, & Pratt, 1996), which has a specific sensitivity to longer wavelengths of light (red) that suppresses activation of the M calls (Kruger, 1977). Red light also impairs the visual-perceptual functions of the M channel, including the perception of motion, global shape and flicker perception (Michimata, Okubo, & Mugishima, 1999; Stromeyer, Chaparro, Tolias, & Kronaver, 1997). The activity of the M pathway increases with the removal of red light (Lehmkuhle, 1993) with reading performance improving when red light is removed by the use of blue filters (Iovino, Fletcher, Breitmeyer, & Foorman, 1998; Solan et al., 1997). Chase et al. (2003) conducted a series of studies which found that the accuracy of oral reading was poorer when using red filters in comparison to blue and green filters, which confirmed the physiological evidence that red light suppresses functioning of the M pathway. Irlen's (2003) survey of coloured filter users found that blue and blue-green are frequently used to reduce the symptoms of IS, which should improve M pathway activities as longer wavelengths (red) would then be absent (Chase et al., 2003).

Coloured filters have been reported to improve eye movement while reading (Evans et al., 1999; Northway, 2003; Robinson & Foreman, 1999a), and lead to changes in visual evoked potentials for people with symptoms of IS (Lewine 1999; Riddell et al., 1998). Numerous controlled studies have also reported improvements in reading with the use of coloured filters. These studies have reported improvements in reading when using coloured plastic overlays, coloured computer monitors and when illuminating text with coloured light (Bouldoukian, Wilkins, & Evans, 2002; Chase et al., 2003; Croyle, 1998; Evans & Joseph, 2002; Jeanes et al., 1997; Noble, Orton, Irlen, & Robinson, 2004; Northway, 2003; Scott et al., 2002; Solan et al., 1997; Solan, Ficarra, Brannan, & Rucker, 1998; Tyrrell, Holland, Dennis, & Wilkins, 1995; Wilkins, Jeanes, Pumfrey, & Laskier, 1996; Wilkins & Lewis, 1999; Wilkins, Sihra, & Myers, in press; Wilkins, Lewis, Smith, Rowland, & Tweedie, 2001; Williams, Le Cluyse, & Littell, 1996). There have also been numerous controlled studies which report improvements in eye strain, headaches, and reading achievement when using coloured lenses (Chronicle & Wilkins, 1991; Evans, Patel, & Wilkins, 2002; Good, Taylor, & Mortimer, 1991; Harris & MacRow-Hill, 1999; Irvine & Irvine, 1997; Lightstone, Lightstone, & Wilkins, 1999; Robinson & Conway, 2000; Robinson & Foreman, 1999b; Wilkins, 1993; Wilkins, Patel, Adjamian, & Evans, 2002). A number of studies have used placebo controls (Bouldoukian et al., 2002; Evans & Joseph, 2002; Jeanes et al., 1997; Robinson & Foreman, 1999a, b; Wilkins et al., 1994; Wilkins & Lewis, 1999; Wilkins et al., 2002). Not all studies, however, have reported improved reading achievement (Fletcher & Martinez, 1994; Martin, MacKenzie, Lovegrove, & McNicol, 1993), which is to be expected, as reported improvements in print clarity may make word recognition easier, but may not lead to the development of word recognition skills without additional reading tuition (Kyd, Sutherland, & McGettrick, 1992; Robinson & Foreman, 1999b).

Irlen Syndrome and Fatty Acid Metabolism

Recent investigations of causal factors for dyslexia have implicated the abnormal metabolism of fatty acids (MacDonnell, Skinner, Ward, Glen, Glen, McDonald et al., 2000; Richardson, Cox, Sargentoni, & Puri, 1997), with visual processing in particular likely to be affected (Richardson, Calvin, Clisby, Schoenheimer, Montgomery, Hall et al., 2000; Richardson, Easton, McDaid, Hall, Montgomery, Clisby et al., 1999; 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) also found the degree of severity of clinical signs of fatty acid deficiency was strongly correlated with visual problems and visual symptoms when reading. Wilmer and Richardson (2001) 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. Essential fatty acids (EFA) play a primary role in most cell signalling systems in neurones and are fundamental to neuronal structure, growth, remodelling and function (Horrobin, 1999). The key EFAs need to come from diet (Holman, 1992), with the level of n-3 fatty acids in the brain being dependent on diet (Makrides, Neumann, Summer, Pater, & Gibson, 1995; Neuringer, Reisbick, & Janowski, 1994). 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 has also been evidence to suggest that supplementation with essential fatty acids may improve retinal and neural function, as well as enhance reading achievement. 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 et al., 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 et al., 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). Richardson, Cyhlarova, Montgomery, Lowerson, & Portwood (2004) found significant improvements in reading and spelling progress for children with a coordinator disorder, which shows a high overlap with dyslexia, when treated with Omega 3 and Omega 6 fatty acids. Richardson, Taylor, Montgomery, Calvin, Schoenheimer, Hall et al. (2001) also found reading improvement in children with dyslexia when treated with the same fatty acids.

The large size of M neurons and their thick insulating coats of the fatty acid substance myelin allow them to carry electrical impulses faster than other nerves (Tallal, 2000), with myelin considered to be particularly important for the efficient functioning of neurones in the MT area of the visual cortex (Klingberg, Hedehus, Temple, Salz, Gabrieli, Moseley et al., 2000), which specialises in motion detection and has been identified as impaired in poor readers (Slaghuis & Ryan, 1999; Talcott et al., 2000). Speed is likely to be a crucial aspect of visual processing in reading, and 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. If the movement of eyes from one focus point to the next while reading takes 20 to 40 milliseconds, but impulses along the M pathway to stimulate saccadic suppression (Hussey, 2002) take 50 milliseconds to activate, then there is likely to be a potential overlap of word images between consecutive eye fixations, as suggested by the M deficit theory.

It has also been hypothesised that defects in detecting rapidly changing auditory signals play a direct role in phonological development, with many of the acoustic signals critical for detecting phonemic segmentation in speech occurring in tens of milliseconds (Poldrack, Temple, Protopapas, Nagarajan, Tallal, Merzenich et al., 2001; Tallal, 2000). Klingberg et al. (2000) found differences in white matter micro-structure between poor and normal readers which they hypothesised could affect the rapid communication between brain areas and the coordination of visual and auditory stimuli necessary for skilled reading. These differences were claimed to be affected by several factors, including the thickness of neurons and the amount and integrity of myelin. The fatty acid substance myelin is thus considered important for rapid conduction of action potentials, with disturbances in myelin being considered detrimental to accurate coding and transmission of rapidly changing visual and auditory stimuli.

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 a number of amino and organic acids. 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. There was 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. A further study (Sparkes, Robinson, Dunstan, & Roberts, 2003) investigated both children and adults with symptoms of IS. The IS group had lower mean levels than the control group for most n-3 and n-6 essential fatty acids. Cholesterol levels were also decreased for the IS group and lower cholesterol levels can be a marker of infection, which in turn may influence the supply of fatty acids. There was also a significant increase in the odd-chain fatty acid, heptadecanoic acid, which has implications for neural transmission and can be an indicator of viral or bacterial infection.

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, 2001) were confounded by the presence of other disabilities, with subjects in the Robinson et al. (1999, 2001) studies

having a primary diagnosis of CFS. A study was thus undertaken of both adults and children with symptoms of IS which were not confounded by other medical conditions that may confuse the interpretation of biochemical profiles.

THE PRESENT STUDY

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 study sample involved 25 subjects (mean age = 22 years) with symptoms of IS and 37 age- and sex-matched controls with no symptoms of IS (mean age = 22 years). The subjects ranged in age from 10 years to 44 years, with 44% being male. 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. In this study a rating of degree of symptoms of IS and degree of improvement when using coloured filters also occurred. These ratings occurred for four areas of symptoms of IS: (1) eye strain/fatigue/headaches while reading; (b) print distortions/clarity while reading; (c) photophobia/light sensitivity while reading; and (d) reading speed and accuracy/duration of reading. The rating sheet used is outlined in Appendix A.

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 et al. (1995) and Tyrrell et al. (1995) have found significant differences in scores on all sections of the manual between reading disabled and normally achieving students. Gray (1999) reported high internal validity for subsections of the manual, as well as significant relationships between scores on the manual and standardised measures of reading achievement, spelling achievement and visual processing. High test-retest reliability for the coloured lenses chosen to most reduce visual distortions has been documented by Robinson and Foreman (1999b) over periods of 8 to 20 months of use. An estimate of the consistency of preferences for coloured overlays reported to most reduce visual distortions was also undertaken by Jeanes et al. (1997) and Wilkins et al. (2001), although the coloured overlays used were different to those developed by Irlen. They found that such preferences for school age children were highly reliable on reassessment, despite different techniques and examiners. The preferences were far more consistent than could reasonable by expected on the basis of chance alone. Wilkins (1997) also assessed the reliability of choice of coloured filters for children and adults over periods of six months to two years of use, with a much higher consistency again being obtained than could be expected on the basis of chance.

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.

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 as outlined in Table 1.

Table 1
Significant differences in the urinary excretion of amino acids between control and IS groups

Urinary Metabolite	t-test P value
Increased (percentage)	
Alanine	<0.02
Phenylalanine	<0.03
Glycine	<0.03
CFSUM1	<0.03
Serine	<0.04
Decreased (concentration)	
Ornithine	<0.05

n=25 and 37 for IS and control subjects respectively

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 is also a precursor of glycine, which functions as a neurotransmitter. 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 higher excretion of phenylalanine for the IS group corresponds with findings by Aldred, Moore, Fitzgerald, and Waring (2003) of significant differences in levels of phenylalanine and alanine in people with autism spectrum disorder when compared to controls. Knivsberg, Reichelt, and Nødland (2001), Richardson and Ross (2000), and Bell, Sargent, Tolcher, and Dick (2000) suggest that biochemical anomalies may play a common role in disabilities, such as dyslexia, ADHD and autism spectrum disorder. Phenylalanine has also been shown to be increased in both plasma and urine as a result of infection and trauma (Wannermacher, Dinterman, Pekarek, Bartelloni, & Beisel, 1975; Wannemacher, Powanda, & Dinterman, 1974). Wannemacher et al. (1975) found that humans experimentally infected with the Sandfly Fever virus, had significantly increased plasma and urinary concentrations of phenylalanine. Phenylalanine loss from muscle increases during infection, but due to an inability of the peripheral tissues to use it, phenylalanine levels build up (Wannemacher, 1977).

An analysis was undertaken of the relationship between the severity of core symptoms of IS (print distortion, eye strain and fatigue, photophobia, and reading difficulties) (Appendix A) and the degree of improvement in these symptoms with the use of coloured filters. This analysis found significant correlations between the core symptom of print distortion and some urinary metabolites, as outlined in Table 2.

Table 2
Significant positive correlations between urinary metabolites and the core IS symptom of print distortion for the IS group

Print Distortion	Metabolite (%)	Spearman R	P-value
Severity	3-methylhistidine	0.62	<0.0009
	1-methylhistidine	0.57	<0.004
	lysine	0.40	<0.05
Improvement	1-methylhistidine	0.55	<0.005
	3-methylhistidine	0.52	<0.009
	lysine	0.42	<0.04

Spearman rank order correlation analysis

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). The higher incidence of mouth ulcers in the IS group in this study (Table 7) could also be an indicator of infection. While recurrent mouth ulcers have numerous causes, they can be indicators of viral reactivation (McGregor et al., 2002). Lysine is found within connective tissue and could indicated connective tissue damage. Increases in lysine may also indicate an overgrowth of gut bacteria that produce lysine.

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, 2000). 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, Lee, Dixon, Blamire, Thompson, Styles et al., 1998; Taylor & Richardson, 2000).

There were also significant differences between experimental and control groups in a number of serum lipids, as outlined in Table 3, with significant correlations between plasma lipids and the core IS symptoms of print distortion and photophobia, as shown in Table 4.

Table 3
Significant differences in the relative abundance of plasma lipids for Juvenile Control and IS Groups

Lipid component	**Control** (mean±SEM)	**IS** (mean±SEM)	**t-test P value**
Heptadecanoic acid (C17:0)	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.

Table 4
Significant correlations between plasma lipids and the core IS symptoms of print distortion and photophobia for the juvenile IS group

Symptom	**Lipid**	**Spearman R**	**P-value**
Print distortion (severity)	sitosterol (%)	0.70	<0.01
	glyceric acid (%)	-0.59	<0.04
Print distortion (improvement)	sitosterol (%)	0.63	<0.03
	glyceric acid (%)	-0.56	<0.05
Photophobia (severity)	total cholesterol	-0.56	<0.05

Spearman rank order correlation analysis

The significant difference in heptadecanoic acid (C17:0)between IS and controls for juvenile groups (below 18 years of age) 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) and Sparkes et al. (2003). Horrobin (1999) has suggested that when essential fatty acids in brain phospholipids are lowered, an increase in saturated fatty acids may worsen conditions such as schizophrenia. Odd-chain fatty acids, such as heptadecanoic acid, may also lead to alterations in the composition of cell membrane lipids and would have implications for neurotransmission.

Differences in heptadecanoic acid may also point to the presence of infection. In a study of cultured human retinal pigment epithelium, which was persistently infected with the rubella virus, there was an increase in odd-chain fatty acids not usually occurring in human cells and increased levels of saturated fatty acids (Williams, Lew, Davidorf, Pelok, Singley, & Wollinski, 1994). The researchers concluded that the resultant changes in fatty acid composition, including increased odd-chain fatty acid abundance, would alter membrane fluidity and therefore cellular function.

A significant reduction in total plasma cholesterol was also found for the IS group of juveniles in comparison to the controls, with the majority of the IS subjects having cholesterol levels below the control group mean, as found in the Robinson et al. (2001) study. In the human brain cholesterol is a significant component, with most of this cholesterol being found within myelin (Snipes & Suter, 1997). It is thought that during disease, the highly myelinated magnocells would be more susceptible to cellular malnutrition (in comparison to cells of the parvocellular pathway) due to their relatively high metabolic requirements. The magnocellular pathway is selectively compromised in the early stages of a number of diseases (Lehmkuhle, 1993) and deficits within the magnocellular pathway have been implicated as a cause of dyslexia (Stein, 2001) and also as a cause of visual processing problems symptomatic of IS (Chase et al., 2003).

The changes in cholesterol level 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). A decrease in total cholesterol levels within human serum has been demonstrated in response to human leucocyte interferon (Dixon, Borden, Keim, Anderson, Spennatta, Tormey, & Shargo, 1984); interferon being produced in response to viral infection. 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.

There were also significant correlations between the core IS symptom of print distortion and both sitosterol and glyceric acid (Table 4). Sitosterol has a similar structure to cholesterol and may be an indication of alterations in gastrointestinal tract absorption, which may have implications for absorption of other nutrients. Glyceric acid is a component of cell membrane phospholipids. The negative association between glyceric acid and print distortion may indicate an increase in phospholipid turnover which has implications for neural transmission. MacDonnell et al. (2000) found abnormally high levels of phospholipase A2 in people with dyslexia, which is part of the metabolic cycle that strips fatty acids from cell membranes.

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 well as a significant increase in the total abundance of saturated fatty acids (Table 5). As saturated fatty acids may compete with EFAs for incorporation into membrane phospholipids, the significant increase seen in saturated fatty acid levels within the IS group may be seen as supporting the result of previous studies, which have found increasing evidence of an association between dyslexia and abnormal fatty acid metabolism (Richardson et al., 1997, 2000, 2001, 2004), especially for visual processing problems (Richardson et al., 1999, 2000, Stordy, 1995). Deficiencies in EFAs have also been associated with retinal malfunction (Birch et al., 1998; Neuringer et al., 1994), as well as magnocellular deficits (Taylor & Richardson, 2000), and both these problems have been hypothesised as causes of IS.

Table 5
Total plasma lipids for juvenile IS and control groups

Lipid Component	Control (mean ± SEM)			IS (mean ± SEM)			P-value
n-6 Fatty Acids	16.03	±	0.46	15.24	±	0.79	NS
n-3 Fatty Acids	0.45	±	0.09	0.31	±	0.08	NS
Saturated Fatty Acids	17.06	±	0.50	19.16	±	0.86	0.02
Sterols	42.59	±	0.80	41.66	±	1.61	NS

The present study aimed not only to investigate possible changes in biochemistry in IS, but to also develop a more objective diagnostic tool to aid in the identification of people with IS, especially young children. The capacity of biochemical profiling to identify both juveniles and adults with symptoms of IS was calculated by standard discriminant function analysis. The discriminant function classified the subjects as either adult IS, adult control, juvenile IS or juvenile control with an accuracy of 87% ($p<0.006$), as outlined in Table 6. The results also identified the primary metabolites used in discriminating between IS and control subjects as the amino acids alanine and ornithine, as well as Urinary Marker 27, an undescribed marker previously identified in subjects with CFS. Alanine is involved in numerous metabolic processes, as discussed in relation to Table 1. Urinary Marker 27 has been associated with the carriage of staphylococci, which are known to produce membrane damaging toxins.

Table 6
Standard discriminant function analysis of differences in urinary amino acid profiles (metabolite concentration)

Model Statistics				
Wilks' Lambda = 0.04, $p<0.0052$				
Classification accuracy (%)				
Adult Control	Adult IS	Juvenile Control	Juvenile IS	Total
84.21	91.67	83.33	92.31	87.10

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). The most common method of identifying children with learning disabilities is a "wait to fail" approach (Flowers, Meyer, Lovato, Wood, & Felton, 2001), with many children not identified until Grade 3 (Flowers et al., 2001; McLesky, 1992), and teacher judgement of reading achievement being only 65% accurate (Madelaine & Wheldall, 2002). By Grade 3 many children have experienced significant and prolonged failure and are unlikely to bridge the academic gap between them and their peers (Flowers et al., 2001; Foorman, Francis, Fletcher, Schatschneider, & Mehta, 1998). This inability to "catch up" provides strong evidence that there may be underlying cognitive processing problems related to reading difficulties (Flowers et al., 2001), which would reduce the effectiveness of remedial intervention (Vellutino, Scanlon, & Lyon, 2000). Early identification of underlying processing problems, such as IS, before remedial intervention occurs, would allow more efficient use of educational personnel and more economical allocation of scarce resources. Smart, Prior, Sanson, and Oberklaid (2001) found that 65% of children with early reading difficulties who had remedial assistance, were still reading disabled at age 13-14.

The significant differences between experimental and control groups in reported prevalence of medical conditions, as well as in possible neurological symptoms and mood change 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
mouth ulcers	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	<0.004
Mood Change			
repeated 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 et al., 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 (not reported by any of the control group), as well as in 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 identified by suggestions of recurring infection in studies by Robinson and colleagues (Robinson et al., 1999, 2001) and Sparkes et al. (2003).

The mood change variables, as well as anxiety and depression, might be expected for any person who has experienced reading difficulties and lacks confidence (Maughan, Rowe, Loeber, & Stouthamer-Loeber, 2003). However, while emotional problems are undoubtedly associated with the adverse effects of school performance, Fleming and Offord (1990) found inconsistent links between adolescent depression and school achievement, which suggests that poor readers may have co-morbid emotional problems. Such co-morbid problems may be more prevalent in people with IS. Cotton and Evans (1990) found that children with IS are likely to be more neurotic, anxious and have a lowered self-concept than other children with a reading disability. Conditions that can be associated with IS, such as CFS, also have a comorbidity with major depression and anxiety (Hickie, Davenport, Issakidis, & Andrews, 2002). 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.

These mood changes in people with IS may also be related to alterations in levels of fatty acids. There have been highly significant correlations between rates of clinical depression and levels of seafood consumption (Adams, Lawson, Sanigorski, & Sinclair, 1996; Edwards, Peet, Shay, & Horrobin, 1998; Maes, Smith, Christophe, Cosyns, Desnyder, & Meltzer, 1996; Peet, Murphy, Shay, & Horrobin, 1998; Tanskanen, Hibbeln, Tuomilehto, Vutela, Haukkala, Viinamaki et al., 2001). Seafood consumption can be a proxy measure of fatty acid intake (Hibbeln, 1998). The DHA content of mother's milk (which reflects n-3 fatty acid status) has also been shown to reflect rates of post-partum depression (Hibbeln, 2002). Plasma levels of n-3 fatty acids have also been found to be significantly reduced in a number of replication studies of patients with depression (Edwards et al., 1998). In addition, fatty acids have been effective in the treatment of depression (Peet & Horrobin, 2001; Nemets, Stahl, & Belmaker, 2002) and in raising the depression ratings of people with schizophrenia (Peet, 2002; Peet & Horrobin, 2001). Hibbeln, Umhau, George, Shoaf, Linnoila, and Salem (2000) suggest that the drug and dietary treatments for cholesterol might have lowered both plasma cholesterol and the tissue concentrations of highly unsaturated fatty acids.

DISCUSSION

The differences in plasma lipid and urine biochemistry between experimental and control groups supports the hypothesis of an association between metabolic anomalies and dyslexia. In particular, alternations were found in amino acids and plasma lipids which have implications for altered membrane function and neurotransmission, especially in the area of visual processing (Richardson & Ross, 2000). There were alterations in five key amino acids which are involved in neurotransmission. There were also lower mean levels in most n-3 and n-6 EFAs for the juvenile IS experimental group, and a significant increase in saturated fatty acids. If the fatty acid composition of neuronal membranes is changed, then neurotransmissions may also be altered. Total plasma cholesterol was also significantly decreased ($P<0.05$) for the IS group of juveniles (Tables 3 and 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). In humans, increases in odd-chain fatty acids, such as heptadecanoic acid and cholesterol (Table 3), 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. These changes 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 heptadecanoic acid 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 has been demonstrated in response to interferon (Dixon et al., 1984), with interferon being produced in response to viral infection. In human retinal pigment infected with the rubella virus, there has been found odd-chain fatty acids not usually occurring in human cells and increased levels of saturated fatty acids (Williams et al., 1994). It should be noted, however, that the differences in lipid and urine biochemistry were not as evident in adults as they were in juveniles. This difference could be due to changes in biochemistry with age, as there have been anecdotal reports from diagnosticians of a reduction of symptoms of IS in some people with age. There have also been reports of differences in common choices of colour between adults and children (Evans & Joseph, 2002), which may reflect differences in biochemistry. The lack of significant differences between experimental and control groups in the adult population may also be due to low subject numbers.

Validation of diagnostic categories

The analysis of biochemical anomalies, as undertaken in this study, could be particularly important in the development of more valid diagnostic categories for people with learning disabilities. Comings, Wu, Chiu, Ring, Dietz, and Muhlemann (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. 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. 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 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. Identification and treatment of the “highly visible” disability, ADHD, for example, might mean that the possibility of other disabilities and treatments is not considered.

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. Klasen

(2002) found little consensus in the definition of learning difficulties for 36 research articles, which made comparison of findings difficult.

Immune Disorders, Dyslexia and Irlen Syndrome

Stein (2000) and Galaburda (1997) cite evidence that dyslexics and their families have a greater than normal incidence of autoimmune disorders, while Knivsberg (1997) found 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. 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). 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 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.

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) also found some people who had been exposed 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 infection with influenza significantly impaired 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. A number of studies have found that people with IS have significant problems with similar eye tracking tasks, involving letter and number identification (Evans, Drasdo, & Richards, 1994; Evans, Busby, Jeanes, & Wilkins, 1995; Robinson & Foreman, 1999b), and improved performance on such tasks with the use of coloured filters (Evans et al., 1994; Northway, 2003; Robinson & Miles, 1987; Robinson & Foreman, 1999b; Solan et al., 1998). 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. The same pattern sensitivity test has been reported to cause similar difficulties for people with IS (Evans, Cook,

Richards, & Drasdo, 1994; Evans et al., 2002; Wilkins, 1991), with coloured filters being hypothesised to improve reading through amelioration of pattern sensitivity (Evans et al., 1994).

The reduction in contrast sensitivity in mid-range frequencies in people exposed to estuarine infection, as identified by Shoemaker and colleagues, 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).

Fatty Acid Deficiencies, Visual Dyslexia, ADHD and Schizophrenia

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 EFA (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 (an n-3 fatty acid) has also been demonstrated (Neuringer, Connor, van Petten, & Barstad, 1984), with other studies of the linolenic acid status in animals reporting poor performance on visual discrimination tasks (Lamptey & Walker, 1976; Yamamoto, Saitoh, Moriuchi, Nomura, & Okuyama, 1987). Infants fed a HUFA-rich diet have also demonstrated an improved visual acuity (Birch, Hoffman, Costaneda, Fawcett, Birch et al., 2002).

Richardson et al. (2001) and Richardson et al. (2004) also reported significant improvements in reading for children with dyslexia, or a dyslexia-related condition, when they took a HUFA supplement. The supplementation for the Richardson et al. (2001) study had a greater effect for children scoring high on 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; Willatts & 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, Aman, Turbott, & Manku, 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 double-blind crossover study (Richardson & Puri, 2002) found a significant reduction in attentional difficulties and general behaviour problems with a HUFA supplementation. 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 for dietary treatment of autism (Knivsberg et al., 2001; Knivsberg, Reichelt, Hoien, & Nødland, 2002) and for the use of omega-3 fatty acids in 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. There is evidence to suggest people with schizophrenia have an impaired performance in fine-feature visual spatial perceptual processing (Tek, Gold, Blaxton, Wilks, McMahon, & Buchanan, 2002), with Richardson and Puri (1999) reporting a single case study of a subject with both schizophrenia and dyslexia, in which there was a reduction in visual symptoms when reading (using a measure that had many indicators of IS) and improvements in reading, spelling and visual motion sensitivity when provided EFA treatment.

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 remedial or dietary intervention lead to changes in neural responses, as identified by Uhlig, Merkenschlager, Brandmaier, and Egger (1997) in relation to dietary changes for children with ADHD and Shaywitz, Shaywitz, Blackman, Pugh, Fulbright, Skudlarski et al. (2004) in relation to reading intervention. Shaywitz et al. (2004) found a phonologically mediated reading intervention which improved reading fluency, resulted in significant and long-term changes in brain systems that underlie skilled reading. 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 could 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 rat retina is able to conserve omega-3 and omega-6 polyunsaturates during essential fatty acid deficiency, with the renewal of photoreceptor membranes ceasing.

CONCLUSION

The findings of the present study add to the growing evidence of a biochemical basis for dyslexia and IS. 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 is a complex cognitive task which requires multi-modal processing and neuroimaging studies show a wide spread of brain regions are involved (Demb, Poldrack, & Gabrieli, 2000). 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. External factors, such as stress, may also be an influencing factor, with stress being linked to immune system modulations (Cohen & Williamson, 1991) and infection and stress linked to the metabolism of EFAs (Horrobin, 1990; De Becker et al., 2002).

It is also 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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Appendix A: Assessment of severity of symptoms/degree of improvement

Name:_____ Date: _____

Scores
0 = not at all
1 = a little bit
2 = moderately
3 = quite a lot
4 = extremely

a. Eye strain/fatigue/headaches while reading
- eyes hurt, burn, itch, feel tired
- become tired while reading
- headaches when reading
- have to make an effort to see words clearly

Severity of symptoms	0	1	2	3	4
Degree of improvement	0	1	2	3	4

b. Print distortions/clarity while reading
- words move/double/merge
- words go blurry/fuzzy/shadowy
- words come off the page
- have halos around them

Severity of symptoms	0	1	2	3	4
Degree of improvement	0	1	2	3	4

c. Photophobia/light sensitivity when reading
- fluorescent lighting uncomfortable or too bright
- white patterns and rivers in print
- glare from white page

Severity of symptoms	0	1	2	3	4
Degree of improvement	0	1	2	3	4

d. Reading speed/errors while reading/duration of reading
- word-by-word reading
- skipping/guessing words
- re-reading
- understand what is read
- duration of reading

Severity of symptoms	0	1	2	3	4
Degree of improvement	0	1	2	3	4