INVESTIGATION OF BIOCHEMICAL ANOMALIES IN PEOPLE WITH A VISUAL FORM OF DYSLEXIA: IMPLICATIONS FOR EARLY IDENTIFICATION AND DIETARY INTERVENTION

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Visual Processing Problems and Dyslexia

In the past decade, visual processing in people with dyslexia has become a more accepted area of research, with a variety of visual processing deficits being investigated (Skottun, 2000; Stein & Talcott, 1999; Wilkins & Lewis, 1999; Willows, 1998). 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), and is unrelated to skills normally assessed by an optometric examination (Evans, Busby, Jeanes, & Wilkins, 1995; Evans, Wilkins, Busby, & Jeanes, 1996). 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).

Retinal malfunction has been implicated as a possible cause of the described symptoms, with Grosser and Spafford (1989, 1990) identifying extra peripheral cones in the retinas of subjects with dyslexia, as well as a greater sensitivity to light in peripheral vision (Grosser & Spafford, 1990; Spafford & Grosser, 1991). 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 symptoms of IS showed an organised dipolar pattern with coloured filters 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. Irvine and Irvine (1997) suggested a variety of possible retinal abnormalities, including signal interference between adjacent receptor cells, abnormalities in receptor distribution, and cones of one colour being attached to the nerve system supporting cones of another colour.

The identified symptoms could also be related to a deficit in the magnocellular visual neurological pathway (Demb, Boynton, Best, & Heeger, 1998; Eden, Van Meter, Rumsey, Maisog, Woods, & Zeffrio, 1996), which may cause an overlapping of visual images between consecutive eye fixations when reading (Solman, Cho, & Dain, 1992; Williams & Lovegrove, 1992), and unstable binocular control (Stein & Talcott, 1999). It has been claimed that magnocellular activation may be involved in suppressing the potential overlap of images between eye fixations (which could be related to saccadic suppression), as well as playing an important part in keeping the two eyes steadily fixed on each word (Stein & Talcott, 1999). Subjects with symptoms of IS have poor eye movements (Robinson & Foreman, 1999a; Solan, Ficarra, Brannan, & Rucker, 1998), and frequently report that letters and words may move, merge and change places (Irlen, 1991a). Studies have identified a diminished or delayed evoked potential for poor readers along the magnocellular pathway (Kubova, Kuba, Peregrin, & Novakova, 1996; Livingstone, Rosen, Drislane, & Galaburda, 1991). Eden et al. (1996) and Demb, Boynton, and Heeger (1998) 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. Colour filtering is claimed to influence the functioning ability of the magnocellular pathway (Edwards, Hogben, Clark, & Pratt, 1996; Solman, Dain, & Keech, 1991; Williams, LeCluyse, & Rock-Faucheux, 1992), and has been reported to reduce symptoms of IS (Harris & MacRow-Hill, 1999; Irlen & Robinson, 1996). The magnocellular hypothesis, however, has been questioned with suggestions that the magnocellular system may be insensitive during saccades (Hulme & Hogben, 1997), or that the magnocellular system, not the parvocellular system is suppressed during saccadic eye movements (Skottun & Parke, 1999).

Numerous studies have reported improvements in reading with the use of coloured filters, although it should be emphasised that reported improvements in print clarity may assist learning to read, but are unlikely to lead to the development of word recognition skills without additional reading tuition (Kyd, Sutherland, & McGettrick, 1992; Robinson & Conway, 1994). These studies have reported improvements in reading when using coloured plastic overlays or coloured computer monitors (see Croyle, 1998; Jeanes, Busby, Martin, Lewis, Stevenson, Pointon et al., 1997; Tyrrell, Holland, Dennis, & Wilkins, 1995; Wilkins, Jeans, Pumfrey, & Laskier, 1996; Wilkins & Lewis, 1999), as well as improvements in eye strain, headaches and reading when using coloured lenses (see Good, Taylor, & Mortimer, 1991; Harris & MacRow-Hill, 1999; Irvine & Irvine, 1997; Lightstone, Lightstone, & Wilkins, 1999; Robinson & Conway, 2000; Robinson & Foreman, 1999a, b; Solan et al., 1998).

Visual Processing Problems, Dyslexia and Biochemical Anomalies

Another recent area of investigation which has implications for visual processing deficits and dyslexia is the analysis of biochemical anomalies. Rae, Lee, Dixon, Blamire, Thompson, and Styles et al. (1998) identified significant metabolic anomalies in males with symptoms of dyslexia in the left temporal lobe and right cerebellum. The metabolic anomalies in the
cerebellum were claimed to be consistent with the hypothesis of a magnocellular deficit, as a major part of the visual magnocellular system projects to the posterior parietal cortex.

A number of studies have also suggested an association between essential fatty acids and visual processing problems in dyslexia (Stordy, 1995; 1998). Stordy (1995) identified a failure to adapt in the dark among adults and children with dyslexia, as has also been found in subjects with symptoms of IS (Carroll, Mullaney, & Eustace, 1994). The dietary essential fatty acid intake of members with symptoms of dyslexia was lower than symptom-free family members, and dietary supplementation normalised dark adaptation within one month. A further study (Stordy, 1998) found the use of a fatty acid supplementation for children with dyslexia resulted in claims of improvement in general learning (89%) and speed of reading (74%).

There has also been identification of biochemical anomalies in people with Chronic Fatigue Syndrome (CFS) and the range of symptoms identified for this disability include visual problems and fatigue, which have been reported by subjects with symptoms of visual dyslexia (as identified by IS). McGregor, Dunstan, Zerbes, Butt, Roberts, and Klineberg (1996a, 1996b), and McGregor, Dunstan, Butt, Roberts, Klineberg, and Zerbes (1997) reported that disturbances in urinary metabolite excretion were correlated with physical and psychological symptoms including photophobia, headaches and trouble concentrating, which are common symptoms of IS. Potaznik and Kozol (1992) and Vedelago (1994) also described symptoms in subjects with CFS which are the same as those identified by subjects with IS, including blurring and shadowing of vision, headaches, eye strain, photophobia, decreased span of recognition of words while reading, and difficulty tracking lines of print. Rosenhall, Johannson, and Orndahl (1987, 1996) found abnormal saccades and disturbed smooth pursuit eye movements in large numbers of people with CFS, and similar symptoms have been identified in subjects with IS (Tyrrell et al., 1995).

The results of the above studies suggest that there is an overlap of symptoms of visual dyslexia (IS) and symptoms of CFS. These studies also implicate biochemical anomalies as a possible causal factor in these symptoms. On the basis of these results, a more detailed analysis of these associations has been instigated. This detailed analysis includes two completed studies and a further study which is in the preliminary stages.

**STUDY ONE**

**Method**

The first investigation (Robinson, Roberts, McGregor, Dunstan, & Butt, 1999) involved 143 subjects with CFS who had been identified on a CFS questionnaire as likely to have some symptoms of IS. These subjects all had a metabolic profile of urine samples using gas chromatography and mass spectrometry (McGregor et al., 1996a).

The CFS questionnaire, which was used as the basis for identifying subjects likely to have symptoms of IS, consists of 86 items which assess symptoms in a wide variety of areas, including headaches/migraine, body pain or tenderness, stiffness of joints, depression, lack of motivation, nausea and stomach upset, tiredness or fatigue and stress. Items from the CFS questionnaire considered to be indicative of IS and used as the basis for analysis of biochemical profiles were:

Item 1: Headaches
Item 33: Dislike of strong light or photophobia

Item 55: Trouble concentrating

The urine data (arcsine transformed) and clinical data were analysed using t-tests, Pearson product-moment correlations, multivariant and one-way analysis of variant (MANOVA and ANOVA), and forward stepwise discriminant function or multiple regression analysis. Correction for statistical multiplicity occurred where applicable. Group differences were also assessed using Hotellings $T^2$. These data were processed using Access (Ver.1.1, Microsoft), Excel (Ver.4.0, Microsoft), and Statistica (Ver.4.5, Statsoft, Tulsa).

**Results**

The areas of significant difference in urinary metabolic profiles for subjects who had indications of light sensitivity, headaches and trouble concentrating on the CFS questionnaire are shown in Table 1 below. These results indicate a variety of possible biochemical anomalies, but must be treated with caution as there could be a variety of possible causes for broad descriptive categories such as headaches and lack of concentration.

**Table 1**

**Significant differences in urinary metabolic profiles for subjects with CFS in the specific symptoms are of light sensitivity, headaches and trouble concentrating (N=143)**

<table>
<thead>
<tr>
<th>Chemical</th>
<th>PHOTOPHOBIA</th>
<th></th>
<th>HEADACHES</th>
<th></th>
<th>TROUBLE CONCENTRATING</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage</td>
<td>Excretion</td>
<td>Percentage</td>
<td>Excretion</td>
<td>Percentage</td>
<td>Excretion</td>
</tr>
<tr>
<td>Leucine</td>
<td>$&lt;.04$</td>
<td></td>
<td>$&lt;.0002$</td>
<td></td>
<td>$.05$</td>
<td></td>
</tr>
<tr>
<td>Asparagine</td>
<td>$&lt;.0002$</td>
<td></td>
<td>$&lt;.0002$</td>
<td></td>
<td>$.04$</td>
<td></td>
</tr>
<tr>
<td>Succinic Acid</td>
<td>$.004$</td>
<td></td>
<td>$.02$</td>
<td></td>
<td>$.05$</td>
<td></td>
</tr>
<tr>
<td>UM 15b</td>
<td>$&lt;.0002$</td>
<td></td>
<td>$.007$</td>
<td></td>
<td>$.02$</td>
<td></td>
</tr>
<tr>
<td>Tyrosine</td>
<td>$.00007$</td>
<td></td>
<td>$.05$</td>
<td></td>
<td>$.03$</td>
<td></td>
</tr>
<tr>
<td>Aspartic Acid</td>
<td>$.02$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>$.05$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$.05$</td>
</tr>
</tbody>
</table>


Significant anomalies were found in excretion of a number of amino and organic acids, including markers of protein turnover (leucine, proline, 3-methylhistidine) and catecholamine production (tyrosine, phenylalanine). These anomalies suggested that an alteration in protein and tissue metabolite turnover may be associated with the alteration in visual function. Increases in post-viral tissue turnover can also result in a dysregulation of fatty acid distribution and studies by Knivsberg (1997), Stevens, Zentall, Abate, Kuczek, and Burgess (1996), and Stordy (1995, 1998) have suggested an association between essential fatty acid anomalies, learning problems, and visual problems in dyslexia.

**STUDY TWO**

While the results of Study One need to be seen as a very tentative first investigation, they did provide further evidence of the potential association between biochemical anomalies and symptoms in people with CFS, which could be indicative of a visual form of Dyslexia (IS). Study Two extended this investigation by undertaking a full screening of symptoms of IS in subjects with CFS, as well as an analysis of serum lipids and amino organic acids.

**Method**

A total of 61 adults were identified from the University of Newcastle CFS patient database and screened for symptoms of IS using the Scotopic Sensitivity Syndrome Screening Manual (Irlen, 1991b), with 38 subjects identified to have moderate to high symptoms and 23 identified to have no symptoms or marginal symptoms. In this study a rating of degree of severity of symptoms also occurred as part of section 3 of the screening battery, as well as rating of the degree of improvement when using coloured overlays. These ratings occurred for four areas of symptoms: a) eye strain/fatigue/headaches while reading; b) print distortions/clarity while reading; c) photophobia/light sensitivity while reading, and d) reading speed/errors while reading/duration of reading. The rating sheet used is outlined in Appendix A.

The study subjects all had a metabolic profile of urine and blood samples using gas chromatography and mass spectrometry (GC-MS). All subjects completed a collaborative pain research unit (CPRU) symptom questionnaire. They had previously collected a first morning urine specimen and a blood sample as part of other studies by the method described in McGregor et al. (1996a). Symptom responses and metabolites were compared using Mann-Whitney U-test and Spearman rank-order correlation (non-parametric data), student t-tests and multiple regression and discriminant function analyses (parametric data).

**Results** Factor analysis divided the study subjects into two groups according to degree of symptoms of IS, with one group having a high level of symptoms of IS (N=31), and the other
group having a low level of symptoms of IS (N=30). There was no difference in age or sex between the high symptom group (Mean age=49.2, sd=16.5 years; females=71.0%) and the low symptom group (Mean age=52.7, sd=11.3 years; females=54.0%).

The two factor analysis groups with high or low levels of symptoms of IS were assessed for the prevalence of other symptoms using their scalar responses to the 86 items on the CPRU questionnaire. Table 1 shows the odds ratios for the assessment of symptom prevalence difference between the two groups; both for ratings of severity of symptoms of IS and degree of improvement of symptoms using coloured filters. While there were a variety of symptoms in which the two groups were different, of particular note are the recurring indicators of infection (sore or swollen lymph nodes in groin and neck).

Table 2

Odds ratio of difference in prevalence of symptoms of CFS between high and low symptom IS groups according to severity of symptoms and response to colour

<table>
<thead>
<tr>
<th>Severity of symptoms of IS</th>
<th>Symptoms of CFS</th>
<th>Odds ratio (95% confidence)</th>
<th>Chi²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sore or swollen lymph nodes in your groin</td>
<td>=7.7</td>
<td>=4.83</td>
<td>&lt;.03</td>
</tr>
<tr>
<td></td>
<td>Tinnitus or ringing in your ears</td>
<td>=3.9</td>
<td>=5.15</td>
<td>&lt;.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response to coloured filters</th>
<th>Symptoms of CFS</th>
<th>Odds ratio (95% confidence)</th>
<th>Chi²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sore or swollen lymph nodes in your groin</td>
<td>&gt;30</td>
<td>=11.91</td>
<td>&lt;.0006</td>
</tr>
<tr>
<td></td>
<td>Difficulty with words or language</td>
<td>=20</td>
<td>=13.75</td>
<td>&lt;.0003</td>
</tr>
<tr>
<td></td>
<td>Unrefreshed or prolonged sleep</td>
<td>=8.5</td>
<td>=5.08</td>
<td>&lt;.03</td>
</tr>
<tr>
<td></td>
<td>Poor appetite</td>
<td>=4.3</td>
<td>=5.74</td>
<td>&lt;.02</td>
</tr>
<tr>
<td></td>
<td>Sore or swollen lymph nodes in your neck</td>
<td>=4.1</td>
<td>=5.52</td>
<td>&lt;.02</td>
</tr>
<tr>
<td></td>
<td>Spells of panic or terror</td>
<td>=4.0</td>
<td>=5.40</td>
<td>&lt;.02</td>
</tr>
</tbody>
</table>
The two factor analysis groups with high or low levels of IS symptoms were assessed for variation in blood lipids and urine amino and organic acids. Table 2 shows the areas of significant difference in lipid and urine components between high and low symptom IS groups according to a) indications of severity of symptoms of IS, and b) assessment of degree of improvement with coloured filters. The mean relative abundance and concentrations are summarised, together with the results of multivariate and univariate analysis.

Table 3
Differences in lipid and urine microbiology between low and high symptom IS groups according to severity of symptoms and response to colour

<table>
<thead>
<tr>
<th>Severity of symptoms of IS</th>
<th>Lipid/metabolite</th>
<th>High symptoms</th>
<th>Low symptoms</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%cis-11, 14, 17 - C20:3</td>
<td>0.12 (0.04)</td>
<td>0.07 (0.04)</td>
<td>&lt;.03</td>
<td></td>
</tr>
<tr>
<td>%C17:0</td>
<td>0.24 (0.07)</td>
<td>0.46 (0.41)</td>
<td>&lt;.05</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%Hydroxyproline</td>
<td>0.58 (0.38)</td>
<td>0.38 (0.25)</td>
<td>&lt;.02</td>
<td></td>
</tr>
<tr>
<td>%Proline</td>
<td>1.92 (1.09)</td>
<td>1.40 (0.93)</td>
<td>&lt;.05</td>
<td></td>
</tr>
</tbody>
</table>

Response to coloured filters

<table>
<thead>
<tr>
<th>Lipid/metabolite</th>
<th>High symptoms (positive response)</th>
<th>Low symptoms (negative response)</th>
<th>p</th>
</tr>
</thead>
</table>
There was an increased level in three lipid and two urine components and a reduced level in three lipid and one urine component for subjects with high symptoms of IS. There was an increased urinary excretion of the connective tissue amino acids, proline and hydroxyproline, and a decrease in the actin-degradation amino acid, 3-methylhistidine. In addition the dietary derived fatty acid trans-9-C18:1 or elaidic acid, which has been linked to macular degeneration of the eye (Hammond, Fuld, & Snodderly, 1996) and alteration in membrane functions, was increased in the subjects with high symptoms of IS, who responded positively to coloured lens use. Palmitoleic acid (cis-9-C16:1), which is also implicated in the facilitation of neural functioning, was also increased in the high symptom IS subjects who responded positively to coloured lens use. Similarly the sterols, cholesterol and lathosterol, so important for proper membrane stability and function, were increased in the high symptom IS group.

It should be noted that the ratings of severity of symptoms of IS are more associated with the connective tissue turnover amino acids (see Table 2, hydroxyproline, proline), while ratings of response to the use of colour are more associated with alteration in lipid components that may alter membrane structure or function (see Table 2, trans-9-C18:1, cis-9-C16:1). It would therefore appear that these two effects may be biochemically different, with the coloured lenses appearing to reduce symptoms associated with membrane changes, which are not related to the underlying increase in tissue turnover.

**STUDY THREE**

The preliminary studies described above have identified possible biochemical anomalies related to visual function, but a larger scale study of people who only have symptoms of IS is needed to replicate these results and to allow a more detailed analysis of biochemical profiles. The purpose of Study Three is to investigate subjects who have symptoms of visual processing problems (IS) but not symptoms of CFS. This study is also investigating children as well as adults.
Research Plan, Methods and Techniques

The research will involve 40 subjects with symptoms of IS and 40 age- and sex-matched subjects with no symptoms of IS. The subjects will be 10 years or above in age and will be taken from people referred to the Special Education Centre, University of Newcastle for reading and writing problems. The subjects will all be required to provide a blood sample, as well as a first morning urine sample. All subjects would also be asked to list the drugs and naturopathic remedies taken and dietary changes that they had made during the preceding 4 weeks. The age- and sex-matched subjects with no symptoms of IS will be recruited primarily from people attending the Special Education Centre for diagnosis of learning disabilities, but also from relatives of the IS subjects.

Molecular analysis will involve the metabolic profiling of urine samples and blood plasma lipids using gas chromatography and mass spectrometry (GCMS). The chemical data and data relating to specific symptoms of IS will be analysed using t-tests, multivariant and one-way analysis of variance (MANOVA and ANOVA) and forward stepwise discriminant function or multiple regression analysis.

Expected Outcomes

Identification of a biochemical basis for the specific symptoms of IS would be expected to have the following outcomes:

1. It would help establish the validity of the Syndrome as a visual-perceptual sub-type of dyslexia.
2. It would lead to more effective treatment strategies based on underlying causes rather than behavioural symptoms such as motivation and attention problems.
3. It would allow early identification.
4. Early diagnosis would also allow professionals to better inform parents of the likely implications of this disability for literacy and learning difficulties.

Identification of biochemical anomalies would in particular allow a much earlier identification of children with symptoms of IS, and help contribute to a more accurate identification. Early diagnosis is important for the 10% to 20% of the school population with a reading difficulty, as lack of early reading success can lead to discouragement, a passive learning style and further failure (Wong, 1986). If identification of literacy problems is left until significant failure occurs, then the academic gap between failing students and their peers may be too great to overcome.

DISCUSSION

The identification in the two completed studies of a significant number of adults with symptoms of CFS who also have visual processing problems indicative of IS, corresponds with the findings of other studies that found visual processing anomalies in adults with CFS (Potaznik & Kozol, 1992; Rosenhall et al., 1987, 1995; Vedelago, 1994). The alterations found in these adults’ urinary excretion of amino acids, such as hydroxyproline, proline and 3-methylhistidine, along with increases in lymph node symptoms, support the hypothesis that the dysregulation of protein and tissue turnover may be causally related to an infective agent and an activation of the immune system resulting in visual dysfunction. There were anecdotal reports from patients in Study Two of vision improvement following the use of amino acid supplements and/or antibiotic treatment of co-morbid bacterial problems.
The differences in Study Two between IS and non-IS groups in trans-9-C18:1 and cis-9-C16:1 may indicate macular degeneration of the eye which may be reflected in the unstable eye movement noted in people with IS (Robinson & Foreman, 1999a; Solman et al., 1998). Stein and Talcott (1999) report that eye movement control for many dyslexics is mildly impaired, which could lead to reports of words moving around the page and appearing to merge, as is reported with symptoms of IS. Biscaldi, Gezeck, and Stuhr (1998) also found a significant correlation between poor eye movement control and dyslexia. The differences in trans-9-C18:1 and cis-9-C16:1 between the IS groups may also be indicative of problems in neural functioning. Delays in visual evoked potential along the magnocellular visual neural pathway have been identified in poor readers and in subjects with IS (Lewine, 1999).

The data from these studies suggest that a complex array of biochemical changes are associated with alteration in vision difficulties in the CFS subjects. The data suggests that these changes may be driven by a pathogen (infective agent). However, the host's response to the pathogen are likely to vary and would be under the control of the host genetics and/or other environmental influences. These preliminary data represent only in the beginning of understanding of a wide range of disabilities, which at the moment are subsumed under broad diagnostic categories such as dyslexia, specific learning disabilities, ADHD, dyspraxia and CFS. 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. It is further claimed (Comings, Wu, Chiu, Ring, Dietz, & Muhleman, 1996) that the underlying cause may be genetic and there may be an additive effect, with a number of genes affecting a range of neurotransmitters. The possibility of overlapping categories of diagnosis for a variety of disabilities has also been put forward by Cohen (1994), Rasmussen and Gillberg (1999), and Anderson (1997). As causal mechanisms for these disabilities become better understood, it is likely that the wide range of symptoms described by each of these broad diagnoses will be broken down into numerous sub-categories, or even separate diagnostic entities, each related to a few specific symptoms that have a common biological/biochemical basis.

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, and this profile will 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 patients being exerted 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). A preliminary multivariate statistical analysis of biochemical profiles of people with symptoms of Autism, ADHD and CFS at the Department of Biological Studies, University of Newcastle, Australia has identified clearly different biochemical profiles for each symptom group. All three groups were also clearly different from a control group with no disabilities.

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 subgroups of a disability, being present in any one study population (Torgesen, 1998). As a
consequence, when researchers attempt to compare findings, they are frequently conflicting, due to patient group heterogeneity.

**Dietary Intervention as a Possible Treatment Option?**
The identification of dysregulated metabolism in people with symptoms of IS raises the question of dietary manipulation and food supplementation as an addition to the already established treatments of tinted filters and remedial support. Dietary intervention for people with dyslexia has been successfully undertaken by Stordy (1995, 1998) and Makrides et al. (1995) using an essential fatty acid supplementation. Hammond et al. (1996) identified individual differences in macular pigment density, which they suggested was related to age-related macular degeneration of the eye and macular degeneration has been linked to diet, with individuals who have a low intake of antioxidant-rich foods having a higher risk of macular degeneration (Goldberg, Flowerdew, Smith, Brody, & Tso, 1988). In Study Two there was an increase in the dietary fatty acid, trans-9-octadecenoic acid (elaidic acid), the accumulation of which has been suggested to be associated with macular degeneration. There have also been anecdotal reports from subjects in this study that vision has improved with the use of amino acid supplements following antibiotic treatment.

There have been a variety of other investigations that implicate diet as a potentially important aspect of treatment for people with learning disabilities. Benton (1997) reported a case study in which a glyconutritional supplement, given to a child with dyslexia, resulted in claims of large improvements in reading and writing activities. Dietary intervention has also been shown to have a positive effect for people with ADHD (Boris & Mandel, 1994; Carter, Urbanowicz, Hemsley, Mantilla, Strobel, Graham, & Taylor, 1993; Egger, Carter, Graham, Gunley, & Soothill, 1985; Egger, Stoller, & McEwen, 1993; Knivesberg, Nøland, Reichelt, & Fosse, 2000; Uhlig, Merkenschlager, Brandmaier, & Egger, 1997). Uhlig et al. (1997) found a significant increase in beta brain electrical activity following the ingestion of previously identified provoking foods. Knivesberg et al. (2000) reported on the evaluation of a casein free diet for children with symptoms of ADHD and additional urinary peptide anomalies. Preliminary data has identified a significant reduction in peptide levels, as well as significant improvements in behaviour. Carter et al. (1993) found a significant worsening in ratings of behaviour and in psychological test performance for provoking foods using blinded crossover design. Boris and Mandel (1994), and Egger et al. (1985) used elimination diets to identify those subjects who responded favourably and then challenged the responders with a variety of foods in a placebo-controlled and blinded study. In both cases, there were significant improvements in behaviour on placebo days compared to challenge days. Egger et al. (1993) obtained positive results for a food desensitisation technique using a double-blind, placebo-controlled trial.

There have also been studies of successful dietary intervention for children with symptoms of autism, and reading problems are more frequent than expected in families with autism (Le Couteur, 1988). Increased levels of peptides have been found in urine analyses (Cade, Privette, Fregly, Rowland, Sun, Zele, Wagemaker, & Edelstein, 2000; Knivsberg, Reichelt, & Nøland, 1999; Knivsberg, Reichelt, Nøland, & Høien, 1995; Reichelt, Knivsberg, Nøland, Stensrud, & Reichelt, 1997), some of which may stem from dietary proteins (Reichelt, Ekrenn, & Scott, 1990; Shattock, Kennedy, Rowell, & Berney, 1990). When autistic subjects in the Knivsberg et al. (1995) study were provided with a diet free of gluten and milk proteins, there was a normalisation of urine patterns and peptide levels within one year and significant improvements in social, cognitive, and communicative skills in a four year follow-up. Those subjects who stopped the diet regressed. Reichelt et al. (1990) also found a normalisation of peptide patterns and improvement in social skills after one year of a similar dietary intervention, while Knivsberg et al. (1999) obtained a similar result over two years of intervention and Cade et al. (2000) after three months of intervention. Other studies have also found a reduction in symptoms of autism following dietary changes (Knivsberg,
Reichel, Høien, & Nødland, 1998; Whiteley, Rodgers, Savery, & Shattock, 1999). Preliminary investigations at the University of Newcastle, Australia, have identified altered urinary amino acid and blood lipid profiles which can be influenced by dietary supplementation. There were also increases in long chain fatty acids indicative of poor intracellular processing of these lipids and supplementation with essential fatty acids could be beneficial. Analyses of faecal bacteria indicated that important gut bacteria are often lacking, and sometimes almost absent, with treatment to normalise this bacteria having beneficial results.

The success of dietary intervention in the areas of ADHD and Autism suggest that a greater understanding of biochemical anomalies may also result in dietary intervention being a useful addition to other treatment procedures for IS. The most immediate needs would be to identify whether changes in diet lead to changes in biochemical profiles and to changes in symptoms, as well as to explore how dietary essential fatty acid may relate to alterations in body levels of trans-9-octadecenoic (elaidic) acid. 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.

Possible Immune System Deficiencies?

It has been claimed that there may be an immunological basis for learning problems. These immune mechanism changes may follow two potential mechanisms: 1) in-utero and/or genetic immune changes effecting development; and 2) viral infection induced changes.

In-utero mechanisms are based upon the observation that antigens in the maternal circulation can cross the placental barrier and influence the organisation, migration and subsequent connectivity of neurons (Duane, 1991), thus altering central nervous system structure and consequent physiology, chemistry and function. Humphries, Kauffman, and Galaburda (1990) hypothesised that the finding of fibromyelin plaques in dyslexic subjects may be the result of central nervous system circulation alterations occurring in the last trimester of foetal development or prior to postnatal year two.

Pennington, Smith, Kimberling, Green and Haith (1987) found elevated levels of antibodies in mothers with dyslexic children, and Lahita (1988) found mothers with a particular immune system disability had a higher than average rate of children with learning disorders. Stein and Talcott (1999) 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 in the urine patterns of dyslexics. A number of other authors have also reported an association between immune disorders and dyslexia (Armstrong, Seidel, & Swales, 1993; Bulmer, 1994; Geschwind & Behan, 1982; Hugdahl, 1995; Wood & Cooper, 1992). Chronic Fatigue Syndrome has also been associated with a variety of immune system deficiencies (Dykman, Tone, & Dykman, 1997; Ojo-Amaize, Conley, & Peter, 1994), as well as dysregulation of immune cell numbers and cytokine production (Gupta & Vayevogula, 1991).

The possible association between CFS, visual/ocular problems and immune system dysfunction was also observed in Study Two. The changes in reading ability and response to lens use were associated with indicators of infection as shown by sore or swollen lymph nodes (Table 1), as well as dysregulation of urinary metabolites and fatty acid metabolism, which may be indicative of a reaction to infection (Table 2) (Arao, Sously, Sato, Morishii, Audo, Yamada, Padilla, Uno, Nii, & Kurata 1997; Qavi, Xu, Green, Lusso, Pearson, & Ablashi 1996; Robinson et al., 1999; Singh, Ling, & Yang, 1998).
The high familial incidence of disabilities such as IS (Robinson, Foreman, & Dear, 1996) suggest that a gene mechanism may influence the probability of immune system dysfunction. However, while familial gene traits may influence the probability of familial reading difficulties, the possibility of familial transfer of infective agents is also a distinct possibility. While viruses such as Human Herpes-6 (HHV-6) are not transferred across the placenta, children usually contract HHV-6 infections in the first couple of years of life from other family members. This is important as reactivation of HHV-6 has also been implicated in the development of CFS (Suhadolnik, Reichenbach, Hitzges, Sobow, Peterson, Henry et al., 1994; Suhadolnik, Peterson, O'Brien, Cheney, Herst, Reichenbach et al., 1997). This virus may also play some role in alteration of retinal function. Qavi et al. (1996) showed that HHV-6 was able to infect corneal epithelial cells, whilst Arao et al. (1997) also showed that HHV-6 was able to infect retinal pigment epithelial cells. Significantly, Singh et al. (1998) reported that HHV-6, along with an autoantibody against neuron-axon filament protein, was increased in patients with autism. Thus the alteration in visual processing may be associated with a persistent viral infection by HHV-6.

CONCLUSION

There is growing evidence of a biochemical basis for a visual processing sub-type of dyslexia. 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 an underlying causal mechanism. This task is made harder because of the complex interaction between underlying causes and environmental influences. Different experiences in relation to home and school support, as well as differences in the amount and type of exposure to remedial intervention, may result in very different behavioural symptoms for similar underlying causes. It has also been suggested that biochemical anomalies and/or neural malfunction may operate in a reciprocal causation cycle (Stein & Talcott, 1999), with changes in brain biochemistry leading to alterations in neural functioning, which could lead to further changes in neural functioning. We are only just beginning to recognise and accept the existence of a number of learning and behaviour difficulties, and only just beginning to be aware of the complexity of causal mechanisms and of the complexity of providing effective intervention strategies.
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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
   o eyes hurt, burn, itch, feel tired
   o become tired while reading
   o headaches when reading
   o 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

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

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

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

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

a. Reading speed/errors while reading/ duration of reading
   o word-by-word reading
   o 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