
■ The Magnocellular Theory of Developmental Dyslexia

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Low literacy is termed 'developmental dyslexia' when reading is significantly behind that expected from the intelligence quotient (IQ) in the presence of other symptoms—incoordination, left–right confusions, poor sequencing—that characterize it as a neurological syndrome. 5–10% of children, particularly boys, are found to be dyslexic. Reading requires the acquisition of good orthographic skills for recognising the visual form of words which allows one to access their meaning directly. It also requires the development of good phonological skills for sounding out unfamiliar words using knowledge of letter sound conversion rules. In the dyslexic brain, temporoparietal language areas on the two sides are symmetrical without the normal left-sided advantage. Also brain 'warts' (ectopias) are found, particularly clustered round the left temporoparietal language areas. The visual magnocellular system is responsible for timing visual events when reading. It therefore signals any visual motion that occurs if unintended movements lead to images moving off the fovea ('retinal slip'). These signals are then used to bring the eyes back on target. Thus, sensitivity to visual motion seems to help determine how well orthographic skill can develop in both good and bad readers. In dyslexics, the development of the visual magnocellular system is impaired: development of the magnocellular layers of the dyslexic lateral geniculate nucleus (LGN) is abnormal; their motion sensitivity is reduced; many dyslexics show unsteady binocular fixation; hence poor visual localization, particularly on the left side (left neglect). Dyslexics' binocular instability and visual perceptual instability, therefore, can cause the letters they are trying to read to appear to move around and cross over each other. Hence, blanking one eye (monocular occlusion) can improve reading. Thus, good magnocellular function is essential for high motion sensitivity and stable binocular fixation, hence proper development of orthographic skills. Many dyslexics also have auditory/phonological problems. Distinguishing letter sounds

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depends on picking up the changes in sound frequency and amplitude that characterize them. Thus, high frequency (FM) and amplitude modulation (AM) sensitivity helps the development of good phonological skill, and low sensitivity impedes the acquisition of these skills. Thus dyslexics' sensitivity to FM and AM is significantly lower than that of good readers and this explains their problems with phonology. The cerebellum is the head ganglion of magnocellular systems; it contributes to binocular fixation and to inner speech for sounding out words, and it is clearly defective in dyslexics. Thus, there is evidence that most reading problems have a fundamental sensorimotor cause. But why do magnocellular systems fail to develop properly? There is a clear genetic basis for impaired development of magnocells throughout the brain. The best understood linkage is to the region of the Major Histocompatibility Complex (MHC) Class 1 on the short arm of chromosome 6 which helps to control the production of antibodies. The development of magnocells may be impaired by autoantibodies affecting the developing brain. Magnocells also need high amounts of polyunsaturated fatty acids to preserve the membrane flexibility that permits the rapid conformational changes of channel proteins which underlie their transient sensitivity. But the genes that underlie magnocellular weakness would not be so common unless there were compensating advantages to dyslexia. In developmental dyslexics there may be heightened development of parvocellular systems that underlie their holistic, artistic, 'seeing the whole picture' and entrepreneurial talents. Copyright © 2001 John Wiley & Sons, Ltd.

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INTRODUCTION

I would first like to say how honoured I am to have been invited to give the fourth T.R. Miles lecture on Developmental Dyslexia. I only hope that I can do the occasion justice in these unhappy circumstances.¹ I believe that the theme of my lecture will be very much to Tim Miles' taste because it is about dyslexia as a neurodevelopmental syndrome. Dyslexics have different brains; so their problems are not confined to reading, writing and spelling, but extend to incoordination, left-right confusions and poor sequencing in general in both temporal and spatial domains. These

¹ Less than an hour before he was due to give the lecture, Professor Stein received the news that his mother had died. *Editor.*

weaknesses all have their counterparts in the cognitive domain, so that dyslexics are notorious for having no sense of time and for difficulties with presenting a logical flow of argument. Tim Miles was the first to see that all these characteristics fit together as a syndrome and how this syndrome distinguishes true developmental dyslexics from ordinary 'garden variety' poor readers whose literacy is poor simply because their intelligence quotient (IQ) is low (Miles, 1970, 1983). The magnocellular hypothesis which I am about to describe offers an explanation that links all these threads together and suggests what their neurobiological basis might be.

DIAGNOSIS

Yet there is currently much argument about whether dyslexia is really qualitatively distinct from poor reading due to low IQ. It is suggested that, because all poor readers have similar phonological problems, there is really nothing to distinguish those with low and high IQ (Stanovitch, Siegel and Gottardo, 1997). But this ignores the other characteristics of dyslexic subjects, not to mention the important fact that IQ explains a highly significant proportion (*ca.* 25%) of the population variance in reading (Newman, 1972). Dyslexics are different because they display a distinctive constellation of symptoms; and their reading is significantly lower than would be expected from their IQ. We therefore define a person as dyslexic if their reading is more than 2 standard deviations (S.D.s) behind what would be expected on the basis of their IQ, together with positive additional features such as incoordination, missequencing and left-right confusions, and if there is no alternative explanation such as physical, psychiatric or educational disadvantage. We adhere to this discrepancy definition, particularly for the purposes of remediation, because the children who are most depressed and frustrated by not being able to learn to read are the most intelligent ones who are just as bright as their peers, but then get branded as lazy and stupid. Usually this leads to a downward spiral of lost self-esteem, depression and misery, followed unfortunately all too often by frustration, aggression and delinquency.

INCIDENCE

Using this discrepancy approach, Yule *et al.* (1973) found that the incidence of significant specific reading problems was around 5% in the Isle of White, but over 10% in inner London. We have recently found that 9.4% of a sample of almost 400 primary school children in Oxford were reading 2 S.D.s or more behind what you would expect of their IQ measured from their Similarities or Matrices scores on the British Abilities Scales (BAS), as follows from the research of Thomson (1982). Thus, in the UK there are probably over half a million children between 8 and 16 years old who could be classed as dyslexic. Very few of these will even be identified by their schools, let alone helped. Only 2.5% of all children are judged by the Authorities to require funding for their special educational needs. So only this amount of

money is set aside, and this has to cover not only dyslexia, but much more obvious disabilities such as cerebral palsy, Down's syndrome, blindness and deafness.

NORMAL READING

The requirements of reading are much more onerous than speaking. The vast majority of children teach themselves to speak without any difficulty. Yet a few years later when they come to learn to read they need to be taught how to do it; they do not pick up reading by themselves. Why is reading so much more difficult than speaking? It is because we speak in syllables, but we write in phonemes. Phonemes are not physiologically distinct; normal speech does not easily break down into individual letter sounds (Liberman, Shankweiler and Studdert-Kennedy, 1967). Writing was only invented when it was realized that syllables could be artificially divided into smaller acoustically distinguishable phonemes that could be represented by a very small number of letters. But this is a wholly man made invention which is only a few thousand years old. And until about 100 years ago it did not matter much if the majority of people could not read; the acquisition of reading had no serious selective disadvantage.

Thus reading requires the integration of two different kinds of analysis (Morton, 1969; Castles and Coltheart, 1993; Ellis, 1993; Seidenburg, 1993; Manis *et al.*, 1997). First the visual form of words, the shape of letters and their order in words, which is termed their orthography, has to be processed visually. Their orthography yields the meaning of familiar words very rapidly without the need to sound them out. But for unfamiliar words, and all words are unfamiliar to the beginning reader, the letters have to be translated into the sounds, phonemes, that they stand for, then those sounds have to be melded together in inner speech to yield the word and its meaning. This phonological processing obviously takes much more time, hence it is much slower than the direct visual route.

THE DYSLEXIC BRAIN

Although recent functional imaging studies have made it clear that language is not strictly localized to the left hemisphere in most people as used to be thought, it is clear that the more taxing the language task the more activated is the language system of linked areas that is situated in the left hemisphere. In particular, increasing the phonological demands of linguistic processing increases the activation of the left hemisphere relative to the right (Demonet, Wise and Frackowiack, 1993). The regions of the left hemisphere involved comprise the secondary areas surrounding the left primary auditory cortex in the superior temporal gyrus (including Wernicke's area and the planum temporale), the supramarginal and angular gyri in the posterior parietal cortex, the insula and the third inferior frontal convolution (Broca's area). However, the homologous areas on the right side are also involved in most language functions, probably mainly for more global processing, for example

for detecting syllable and word boundaries, intonation and the emotional content of speech.

Beyond the occipital cortex, visual processing divides into two streams (Ungerleider and Mishkin, 1982). The dorsal one is dominated by magnocellular neurones specialized for detecting visual motion. It is devoted to controlling eye and limb movements and passes into the supramarginal and angular gyri in the posterior parietal cortex. The ventral pathway is specialized for identifying visual form and projects into the temporal cortex. Thus, vision feeds into the language system for reading via both visual outflow pathways from the posterior parietal and from the temporal cortex; hence functional imaging studies consistently show activation of these regions during reading.

Studies of dyslexic brains have, therefore, shown the most striking differences in these areas. Studying brains of known dyslexics post mortem, Galaburda *et al.* (1978) found that the normal asymmetry of the planum temporale favouring the left side tends to be absent in dyslexics (and this has been confirmed by structural imaging studies *in vivo*, though denied by some). Furthermore, Galaburda found abnormal symmetry in the posterior parietal cortex of dyslexics as well. Finally he observed small aberrant 'brain warts' (ectopias) clustered around the temporoparietal junction (Galaburda and Kemper, 1979). These are small outgrowths of cortical neurones through the outer limiting membrane that occur early in the development of the brain at about the fifth month of foetal life. They are associated with widespread disruption of the normal connections. In particular, a greater number of axons than normal survive that cross in the corpus callosum to homologous areas in the opposite hemisphere. It is not surprising, therefore, that there are numerous functional imaging studies that show deficiencies of the activation of these areas in dyslexics compared with good readers when they undertake reading tasks. Perhaps not so expected, but relevant to my topic, is the discovery by my ex-student, Guinivere Eden, that many dyslexics have reduced activation of visual areas in the dorsal stream in response to moving visual targets (Eden *et al.*, 1996).

VISUAL MAGNOCELLULAR SYSTEM

At first sight, reduced sensitivity to visual motion may seem to have nothing to do with reading. But it indicates reduced sensitivity of the visual magnocellular system. A total of 10% of the ganglion cells whose axons provide the signals that pass from the eye to the rest of the brain are noticeably larger (*magno*—larger in Latin) than the remainder (*parvo*—smaller in Latin) (Enroth-Kugel and Robson, 1969; Shapley and Perry, 1986). This means that they gather light from a larger area so that they are more sensitive and faster reacting over a larger area, but not sensitive to fine detail or colour (Maunsell, Nealey and DePriest, 1990; Merigan and Maunsell, 1993). They project to the primary visual area in the occipital cortex via their own private magnocellular layers in the main relay nucleus, which is called the lateral geniculate nucleus (LGN). Although there is mingling of magno and parvo inputs in the primary visual cortex, the dorsal visual processing stream is

dominated by input from the magnocellular system. Hence, the dorsal stream plays a major role in the visual guidance of eye and limb movements (Milner and Goodale, 1995), and it projects onwards to the frontal eye fields, superior colliculus and cerebellum, which are all very important for visuo-motor control.

DYSLEXICS' VISUAL MAGNOCELLULAR SYSTEM

One advantage of the separation of the visual magno- and parvocellular systems is that their sensitivity can be assessed psychophysically in normal subjects using stimuli that selectively activate one or the other. Spatial contrast and temporal flicker sensitivity are limited mainly by the performance of the peripheral visual system up to the level of the visual cortex. Lovegrove *et al.* (1980) therefore used sinusoidal gratings to show that the contrast sensitivity of dyslexics was impaired compared with controls, particularly at low spatial and high temporal frequencies. So he suggested that dyslexics may have a selective impairment of what was then called the visual transient system. He also found that, at the high spatial frequencies that are mediated by the parvocellular system, the contrast sensitivity of his dyslexics was actually higher than in controls and we confirmed this in dyslexics who suffer visual symptoms (Mason *et al.*, 1993). That they actually performed better at high spatial frequencies shows that the dyslexics were not simply bad at all visual tests.

Martin and Lovegrove (1987) also showed that dyslexics' flicker sensitivity tends to be lower than controls, and we have confirmed this too (Talcott *et al.*, 1998). All these findings suggest that dyslexics may have a specific impairment of their visual magnocellular system (Livingstone *et al.*, 1991; Stein and Walsh, 1997; Stein and Talcott, 1999). However, this conclusion has been hotly disputed (Skottun, 2000, but see Stein, Talcott and Walsh, 2000a). The impairment is slight and is not found in all dyslexics. Hence, some studies that have used only small numbers of subjects have failed to replicate Lovegrove's results. Much larger numbers are needed to confirm the peripheral magnocellular impairment, together with prescreening dyslexics for those who have visual symptoms and, therefore, are most likely to have a significant magnocellular deficit.

As we have seen, magnocellular neurones are also found in the occipital cortex. They are most reliably activated by moving visual stimuli. Hence, testing sensitivity to visual motion has proved a more consistent way of showing the magnocellular deficit in dyslexics because motion engages not only the peripheral magnocells, but also central processing stages up to at least area V5/middle temporal (MT) visual area in the central cortex. In monkeys, it has been found that detecting coherent motion in a display of dots moving about randomly (random dot kinematograms—RDK) is a sensitive test for probing the whole magnocellular system (Newsome and Pare, 1988; Newsome, Britten and Movshon, 1989).

We have, therefore, developed a RDK test of motion sensitivity for use with adults and children. We present two panels of randomly moving dots side by side. In one of the panels, selected at random, a proportion of the

dots is moved together 'coherently' so that they look like a cloud of snowflakes blown in the wind. The subject is asked in which panel the cloud appears to be moving. The proportion of dots that is moved together is then reduced until the subject can no longer tell on which side the dots are moving together. His threshold is then defined as the proportion of dots that have to move together for him to see the coherent motion correctly on 75% of occasions. Using this test, we have found that in both children and adults whose reading is significantly behind that expected from their age and IQ, a high proportion have worse motion sensitivity than controls matched for age and IQ (Cornelissen *et al.*, 1994, 1994b; Talcott *et al.*, 1998, 2000b). This conclusion from psychophysical studies that many dyslexics have poor motion sensitivity has been confirmed by other labs (e.g. Eden *et al.*, 1996; Demb *et al.*, 1998) by electrophysiological studies (Livingstone *et al.*, 1991; Maddock, Richardson and Stein, 1992; Lehmkuhle and Williams, 1993) and by a succession of functional imaging studies (Eden *et al.*, 1996; Demb, Boynton and Heeger, 1997).

It is still argued, however, that poor readers might simply be bad at all psychophysical tests, and that there is nothing specific to their visual magnocellular system. Their superior performance at high spatial frequencies, which are not processed by the magnocellular system, is one argument against this view. But not all research has confirmed this, as we have seen. We have, therefore, developed a control 'form coherence' test that is almost identical to the motion test, except that the random elements are stationary, not moving. They form a series of concentric circles and we reduce the proportion forming the circle until it can no longer be seen. The dyslexics were as good as the fluent readers at this task, confirming that it is specifically the movement in the motion coherence task at which they are impaired, in other words that it is only their magnocellular system which is affected.

THE DYSLEXIC LGN

The most direct evidence that many dyslexics have impaired development of the visual magnocellular system was again provided by Galaburda and colleagues examining the brains of dyslexics post mortem. They found that the magnocellular layers of the LGN of the thalamus were disordered, and the neurones were some 30% smaller in area than in control brains (Livingstone *et al.*, 1991; Galaburda and Livingstone, 1993). As with the ectopias, these differences are known to arise during the early development of the brain, during the phase of rapid neuronal growth and migration during the 4th or 5th month of foetal development. One could not adduce stronger evidence than this that the visual magnocellular system fails to develop quite normally in dyslexics.

We have also investigated whether, overall, the receptive fields of dyslexics' visual magnocells are reduced in size by varying the number of dots per unit area (the dot density) of our RDKs. Whereas the sensitivity to visual motion was unaffected except at very low densities in good readers, that of dyslexics fell off at much higher densities, suggesting that their

magnocellular neurones were undersampling the dots spatially, i.e. that their receptive fields were effectively smaller (Talcott *et al.*, 2000b).

MAGNOCELLULAR SENSITIVITY AND ORTHOGRAPHIC SKILL

It is not immediately obvious how the visual magnocellular system contributes to reading, however, since print is usually stationary, not moving, when you are trying to read it. So there is still scepticism about whether the magnocellular impairment, even if it exists, has anything to do with reading (Hulme, 1988). It might be an epiphenomenon connected with the dyslexic phenotype, but playing no important causal role in dyslexics' reading difficulties. Causation is very difficult to prove completely; indeed some philosophers would say that it is impossible.

Breitmeyer (1993) suggested that magnocellular activity during each saccade is necessary to erase the parvocellular products of the previous fixation; hence weak magnocellular responses might fail to do so and the letters seen on the previous fixation might superimpose on those derived from the next fixation. However children tend to confuse neighbouring letters, not those separated by 6 or 7 mm, which is the distance covered by reading saccades. Furthermore, it has been shown that magnocellular activity does not inhibit parvo during saccades (Burr *et al.*, 1993); hence Breitmeyer's explanation is unlikely.

Nevertheless, there are plenty of other potential causal connections between visual motion sensitivity and reading. The magnocellular system is known to be important for direction of visual attention and, therefore, of eye movements, hence for visual search also. All three have been shown to be worse in dyslexics (Stein and Walsh, 1997; Everatt, 1999; Iles, Walsh and Richardson, 2000). Thus, we have been amassing more and more evidence that there is a causal connection between magnocellular function and reading. The first step was to show not just that dyslexics have poor magnocellular sensitivity, but to demonstrate that individuals' magnocellular sensitivity specifically predicts the quality of their visual reading abilities, their orthographic skill. We first showed this by comparing the visual motion sensitivity not only of dyslexics, but also of good and average readers with their ability to spell irregular words (Castles and Coltheart, 1993). English has many 'exception', irregularly spelt, words, such as yacht, whose spelling cannot be obtained by sounding them out; instead their orthography must be remembered visually. We found that people's visual motion sensitivity correlates best with their ability to spell such irregular words. For instance, in a class of 10 year old primary school children their visual motion sensitivity accounted for as much as 25% of the variance in their irregular word reading (Talcott *et al.*, 2000a).

An even more specific measure of orthographic skill is the pseudo-homophone test (Olson *et al.*, 1989). In this, two words that sound the same but have different spellings are presented side by side, i.e. 'rain' beside 'rane', and the subject is asked which is the correct spelling. Since the words sound exactly the same, this task cannot be solved phonologically by sounding out the letters; instead the visual form, orthography, of the word

must be recalled correctly. Again we found that the correlation between visual motion sensitivity and performance in this pseudo-homophone test was very strong (Talcott *et al.*, 2000a), and again this was true not only in dyslexics, but across the whole range of reading abilities. Good spellers in this test had high motion sensitivity, whereas poor performers had low motion sensitivity.

In contrast, the correlation between subjects' visual motion sensitivity and tests of phonological skill, such as the ability to read nonsense words or to make Spoonerisms was much lower. In fact, when we controlled statistically for the correlation that exists between subjects' phonological and orthographic abilities, we found that motion sensitivity continued to account for a high proportion of the residual variance in orthography, but now of course independently of phonology (Talcott *et al.*, 2000a). In other words, motion sensitivity accounts for children's orthographic skill independently of its relationship with their phonological skill, as you would expect if this basic visual function helps to determine how well the visual skills required for reading develop.

VISUAL PERCEPTUAL INSTABILITY

Nevertheless, however strong the association, correlation does not prove causation. We need to work out the reason why visual motion sensitivity might determine how well people can develop orthographic reading skills, and then to prove each step. Paradoxically, one of the most important uses to which visual motion signals are put is to achieve visual perceptual stability. The eyes are never completely stationary. Hence, images are always smearing across the retina; yet our perception of the visual world is usually crisp and unmoving. The visual motion signals accomplish this stability by two main mechanisms:

The first is 'computational'. Any motion between successive images which are sampled three or four times per second is used to 'morph' one on to the next so that any image movement between samples can be ignored, unless there is a motor signal indicating that the eyes have been moved intentionally. Secondly, larger unintended eye movements are corrected by magnocellular signals. Any motion of images on the retina generated by unwanted eye movements are fed back to the ocular motor system and used to bring them back on target.

BINOCULAR CONTROL

Unintended eye movements are a particular problem when the eyes are converged at 30 cm for reading. Being uncontrolled, the movements of the two eyes are not linked, nor monitored. Hence, the two eyes lines of sight can cross and recross each other, so that objects seen by the eyes can appear to do the same. Normally, the motion signals provided by each eye are fed back to that eye's muscles to keep it on target. This is termed

utrocular control (Ogle, 1962) for which the underlying physiology is gradually being worked out. But we have found that most children with visual reading problems have markedly unsteady binocular fixation which correlates with their visual perceptual instability (Fowler and Stein, 1979; Stein and Fowler, 1980; Stein, Riddell and Fowler, 1988; Stein and Fowler, 1993; Eden *et al.*, 1994), and others have confirmed this (e.g. Bigelow and McKenzie, 1985; Evans, Drasdo and Richards, 1994).

POOR VISUAL LOCALIZATION

The steadiness with which children can fixate with their two eyes correlates well with the sensitivity of their magnocellular systems to visual motion as one might expect. Hence, the quality of their binocular fixation determines how steady the letters appear when they are trying to read them. Thus a child's visual motion sensitivity dictates their ability to determine the correct order of letters in a word. For example, children with low magnocellular function, as evidenced by reduced visual motion sensitivity, are slower and make more errors in judging the correct order of letters in words when viewing briefly presented neighbouring letter anagrams (rain vs. rian—Cornelissen *et al.*, 1997).

If impaired magnocellular function causes perceptual instability as I am suggesting, then this should apply not only to letters in words but to any small visual target in any context. We have, therefore, measured how accurately children with binocular instability can localize small dots presented on a computer screen. As expected, they were very significantly worse at this task than controls (Riddell, Fowler and Stein, 1990).

LEFT NEGLECT

What was even more interesting was that the dyslexics with unstable binocular control were very much worse at locating targets in the left as opposed to the right visual field, whereas the good readers were somewhat better on the left side. This represented experimental confirmation of our somewhat anecdotal earlier observation that many dyslexics with binocular instability showed mild left neglect in their drawings of clocks; they tended to bunch all the figures into the right side and leave the left side of the clock empty (Stein and Fowler, 1981). This theme has been taken up again by Ruta Han, who has confirmed what she has termed left 'mini-neglect' in many dyslexics (Han and Koivikko, 1999). There is a long but somewhat inconclusive literature on the role of hemispheric specialization in dyslexia (Boliek and Obrzut, 1999). Nevertheless, there is quite strong evidence that dyslexics may fail to establish fixed hemispheric specialization. This is revealed by lack of strong right or left handedness, symmetry of the planum temporale, and recent evidence that in dyslexics the normally greater density of white matter in the left hemisphere is reduced (Klingberg *et al.*, 2000).

UNSTABLE VISUAL PERCEPTION

Their own description of what they see when trying to read provides the most convincing evidence of the perceptual instability that many children with reading difficulties suffer. Pringle Morgan's first description of word blindness was of the boy Percy who often spelt his own name Precy, and despite being perfectly bright in other words couldn't work out the order that letters should go in (Morgan, 1896). Two thirds of the children we see have unstable binocular control and complain that the small letters they are trying to read appear to move around, to change places, to merge with each other, to move in and out of the page, to blurr or suddenly get larger or smaller (Fowler and Stein, 1979; Stein and Fowler, 1981; Simons and Gordon, 1987; Garzia and Sesma, 1993). It is no wonder that they cannot work out reliably what order they should be in or lay down reliable memories of their orthography.

We and others have confirmed that these 'anecdotal' accounts really do indicate perceptual instability in a number of studies. Children with binocular instability make more visual errors when letter size is decreased (Cornelissen *et al.*, 1991) and when the letters are crowded closer together (Atkinson, 1991). They tend to produce nonwords that betray that they are misidentifying and misordering letters visually. Hence, they tend to misspell irregular words by attempting to sound them out, making 'phonological regularization' errors (Cornelissen *et al.*, 1994, 1994b). Importantly, because their instability is binocular, their visual confusion may be exacerbated by the two eyes presenting different competing versions of where individual letters are situated. Hence, reading using only one eye with the other blanked will often improve their reading (Fowler and Stein, 1979; Stein and Fowler, 1981, 1985; Cornelissen *et al.*, 1992; Stein, Richardson and Fowler, 2000b).

MONOCULAR OCCLUSION

The most convincing way to show that one phenomenon causes another is to show that changing one changes the other. Thus our demonstration that blanking one eye, monocular occlusion, can improve some children's reading is important evidence that binocular confusion is a significant cause of reading problems. As we have seen, abnormal magnocellular function may cause such binocular instability. Since these eye movements are unintended and uncontrolled, they may be misinterpreted as movements of the letters. Since this instability often causes the two eyes' lines of sight to cross over each other, the letters appear to move around, slide over each other, and change places. This is why simply blanking the vision of one eye can simplify the visual confusion and help these children to see the letters properly. We have repeatedly confirmed this (Stein and Fowler, 1981, 1985; Cornelissen *et al.*, 1992; Stein, Richardson and Fowler, 2000b). In children with binocular instability, occluding the left eye for reading and close work relieves their binocular perceptual confusion and helps them to learn to read. This observation has been made by numerous other workers as well (Benton

and McCann, 1969; Dunlop 1972; Bigelow and McKenzie, 1985; Masters, 1988). The results are often dramatic and, in our most recent double blind controlled trial of monocular occlusion in dyslexic children with binocular instability, we were able to help those who received the occlusion almost to catch up with the reading age of their peers. In contrast, those who did not receive occlusion and who did not gain binocular stability remained lagging 2 years behind their chronological age. This progress is far greater than most remediation techniques achieve with dyslexics.

After 3 months occlusion, not only had the children's reading improved to this great extent, but also they could now fixate stably with their two eyes, so that they no longer needed to wear the patch. This gain of binocular stability is because the period of occlusion enables the magnocellular signals from the seeing eye to be routed to control the muscles of that eye (Ogle's utricular control), after which those from the occluded eye follow suit. This magnocellular utricular control is probably crucial for the final stages of precise vergence fixation because it enables each eye to home in accurately on a target so that both can fixate accurately and steadily on it.

GOOD MAGNOCELLULAR FUNCTION IS ESSENTIAL FOR STABLE BINOCULAR FIXATION

So now we can explain how magnocellular function impacts on reading, and in particular helps to develop orthographic skill. Poor readers have slightly impaired development of their magnocellular neurones. As a consequence, the dense magnocellular input that visuomotor centres in the posterior parietal cortex, superior colliculus and cerebellum receive is both delayed and smeared in time. In consequence, utricular control over the muscles controlling the eye that supplied the magnocellular input is less sharply focussed in time and, therefore, less able to stabilize the eyes during fixation especially when the eyes are converged at 30 cm for reading. Therefore the eyes' lines of sight may cross over each other, hence the letters can appear to do so also. This is why these dyslexics tend to reverse the order of letter features, thus confusing ds with bs and ps with qs, and to reverse the order of neighbouring letters, and make anagram errors. Therefore, helping them to steady their binocular fixation helps them to improve their reading.

AUDITORY/PHONOLOGICAL PROBLEMS

The other main skill required for reading is to be able quickly to produce the sounds (phonemes) that each letter or group of letters stands for. It is generally agreed that many dyslexics fail to develop adequate phonological skills (Lieberman *et al.*, 1974; Lundberg, Olofsson and Wall, 1980; Snowling, 1981; Bradley and Bryant, 1983; Snowling, 1987). Indeed, majority opinion still has it that this is the main, if not the only, problem from which dyslexics suffer and that visual disturbances are very rare. In contrast, we find that in only about a third of dyslexics are their main problems phonological; in about one third their main problems are visual/orthographic; and the

remaining third have both problems in almost equal proportions. But we think that even the phonological problems have a much more fundamental physiological cause. In many ways, it is the auditory analogue of the visual magnocellular impairment that we have been discussing.

SENSITIVITY TO CHANGES IN SOUND FREQUENCY AND AMPLITUDE

Letter sounds consist of relatively slow (2–50 times per second) changes in frequency and changes in speech amplitude. Hence, distinguishing them depends on being able to identify these transients in the speech signal (Tallal, 1980; Moore, 1989). Just as we can measure individuals' visual motion sensitivity using simple random dots, so we can also assess individuals' basic sensitivity to these acoustic cues using much simpler stimuli, namely sinusoidal frequency and amplitude modulations (FM and AM) of a tone. We can, therefore, test psychophysically how much the frequency or amplitude has to be changed for the listener to distinguish the modulated from the pure tone.

As expected, we found that dyslexics as a group are considerably worse at detecting these transients than good readers, i.e. they require significantly larger changes in frequency or amplitude to distinguish them (McAnally and Stein, 1996; Stein and McAnally, 1996; Witton *et al.*, 1997, 1998; Menell, McAnally and Stein, 1999; Talcott *et al.*, 1999, 2000a) and this has been confirmed by other groups (e.g. Dougherty *et al.*, 1998; Han *et al.*, 1999, although they failed to find impairment in one kind of phase locking). Importantly, we showed that the dyslexics were just as good as good readers at distinguishing much higher rates of frequency modulation (240 Hz) that are not used for phoneme detection. These are processed by a different, 'spectral', auditory mechanism (Moore, 1989). Dyslexics' success at these rates shows that they are not simply bad at all auditory tasks, and confirms that they have specific problems just with the modulations that are crucial for distinguishing letter sounds.

FM SENSITIVITY PREDICTS PHONOLOGICAL SKILL

Since we are suggesting that this fundamental sensitivity to auditory transients determines how well people can pick up the acoustic cues distinguishing phonemes, again we need to show that there is a close association between people's FM and AM sensitivity and their phonological skill. The purest test of phonological skill is to get subjects to read nonsense words such as 'tegwop' (Snowling, 1987). The visual form of such words is unfamiliar, yet despite their not meaning anything at all they can easily be sounded out by good readers to yield a pronunciation. Reading them, therefore, depends heavily upon fluent letter sound translation; hence phonological dyslexics are much slower at reading nonwords and they make many more mistakes than normal readers.

We have, therefore, compared readers' auditory FM and AM sensitivity with their ability to read nonwords. The correlation between the two turned out to be strikingly high (Witton *et al.*, 1998; Talcott *et al.*, 1999, 2000a). For instance, in a group of 35 good and bad adult readers their 2 Hz FM sensitivity accounted for over 36% of their variance in nonword reading ability, and in a group of 32 unselected 10 year old primary school children an amazing 64% of their variance in nonword reading ability was accounted for by their 2 Hz FM sensitivity. As expected in both groups, FM sensitivity was more highly correlated with measures of phonological ability than with orthographic abilities.

In order to examine these relationships further, we tested how far FM sensitivity predicted variance in phonological abilities independently of IQ or orthographic ability. We therefore first removed the variance accounted for by their similarities and matrices IQ together with that shared between their phonological (nonword reading) and orthographic (homophone spelling) abilities. Even after this, their FM sensitivity still continued to account for nearly 25% of the residual variance in their phonological skill, now independently of orthographic ability (Talcott *et al.*, 2000a). In other words, it seems that auditory FM sensitivity accounts for unique variance in phonological ability, suggesting that it plays an important part in determining how easily we acquire phonological skill.

Again, however, the idea that basic auditory sensory processing plays any important part in linguistic function is strongly resisted. It is claimed that, since the linguistic processor can extract meaning from very impoverished auditory input, the quality of that input is relatively unimportant (Studdert Kennedy and Mody, 1995). Whilst this may be true of articulate and literate adults facing partial deafness late in life, it certainly is not true of dyslexic children. We have shown that they are highly affected by impoverished acoustic input. For example, they are far worse at deciphering consonants masked in noise (Cornelissen *et al.*, 1995), sine wave speech (Hogg, Rosner and Stein, 1998), or speech in which 100 ms segments have been reversed in time (Witton *et al.*, 1999).

Ideally, however, we would like to clinch the causal argument that poor AM and FM sensitivity prevents the acquisition of good phonological skill by showing that improving children's AM and FM sensitivity by sensory training will help them to acquire phonological skill. We have not tried to do this yet; but Merzenich *et al.* (1996) have found that training children with specific language delay using computer generated phonemes in which the sound frequency changes have been slowed and the amplitude changes have been increased can improve their language performance greatly. It seems likely that these gains might occur in dyslexics given similar training.

SENSORY BASIS OF READING PROBLEMS

It thus appears that we can explain a large amount of the differences in reading ability in terms of basic sensory sensitivity to visual and auditory transients. In our group of 10 year olds, visual motion and auditory FM and AM sensitivity accounted for nearly two thirds of their differences in reading

and spelling ability (Talcott *et al.*, 2000a). This means that the standard of their teaching and sociocultural influences may be less important than was previously thought; their physiologically determined, low level, visual and auditory transient sensitivity is what matters most for the development of their reading skills.

From this follow a number of exciting implications. First as regards remediation, we know that sensory sensitivity can be improved by appropriate training, particularly in young children. So our increased physiological understanding of the basis of reading skills, far from consigning children with sensory weaknesses to permanent illiteracy as some fear, should empower us to help them much more effectively than in the past. For instance, our simple technique of monocular occlusion in appropriate cases costs very little; yet improves children's reading far more than much more costly reading recovery programmes.

Our next plan, therefore, is to modify our transient tests for use with 5 year olds when they first enter school in order to detect any weaknesses. We will then follow the children's reading progress over the next 3 years, and see how far their performance at 5 predicts their success with later acquiring the orthographic and phonological skills required for reading. If, as we expect, their predictive power is good, then we will attempt to improve any weaknesses by appropriate training and see whether this improves their orthography and phonology.

MAGNOCELLULAR SYSTEMS

Only in the visual system do the magnocellular neurones that time visual events and track moving targets form a clearly distinct and separate system. Nevertheless, in all the sensory and motor systems there are large (magnocellular) cells that are specialized for temporal processing. Thus, the neurones in the auditory system which track the frequency and amplitude changes that distinguish phonemes are in the magnocellular divisions of the nuclei which relay auditory signals to the auditory cortex (Trussell, 1998). In dyslexic brains examined post mortem, Galaburda, Menard and Rosen (1994) showed that neurones in the magnocellular division of the medial geniculate nucleus were disordered and smaller than in control brains, suggesting that they too are abnormal in dyslexics.

Also the cells that signal flutter and vibration in the skin are large neurones found in the dorsal column division of the somesthetic system. The largest of these afferent fibres in cutaneous nerves supply Pacinian corpuscles deep in the skin, which are most sensitive to vibration. We have, therefore, tested skin sensitivity to mechanical vibration in dyslexics, and found mild deficits (Stoodley *et al.*, 2000). Grant *et al.* (1999) also found reduced tactile sensation that were consistent with impaired magnocellular dorsal column function in dyslexics.

It seems, therefore, that magnocells in general might be affected in dyslexics (Stein and Walsh, 1997; Stein and Talcott, 1999). In all our studies, we have found that subjects' auditory and visual transient performance tends to be highly correlated; both are good or both are bad. This suggests that there

may be some common underlying factor that determines the development of all magnocells throughout the brain.

The same conclusion is indicated by their neurohistology. Hockfield and Sur (1990) found that there seems to be a system of magnocellular neurones throughout the brain that express a common surface antigen which can be recognized by specific antibodies such as CAT 301. These are found not only in the visual system, but also in the auditory, somaesthetic and motor systems. CAT 301 staining is particularly strong in the cerebellum. It is, therefore, natural to ask whether all these magnocellular systems may be affected in dyslexics.

THE CEREBELLUM

The cerebellum is the brain's autopilot, specialized for automatic preprogrammed timing of muscle contractions for optimizing motor performance. Accordingly, it requires and receives heavy magnocellular projections from all sensory and motor centres. For example, quantitatively the largest output of the dorsal 'where' visual magnocellular route is to the cerebellum via the pontine nuclei (Stein, 1986; Stein and Glickstein, 1992). Likewise, the dorsal spinocerebellar tract is dominated by dynamic signals provided by Group Ia muscle spindle fibres. Furthermore, its Purkinje cells demonstrate some of the heaviest staining with the magnocellular marker, CAT 301. Thus the cerebellum not only receives timing signals from magnocellular systems in other parts of the brain, but also it can be considered itself, perhaps the most important part of the magnocellular timing system of the brain. Actually, I was originally persuaded to study the eye movements of dyslexics by Fowler, because they were so similar to those of patients that I had been studying with lesions of the cerebellum.

Fawcett, Nicolson and Dean (1996) showed that dyslexics perform worse than normal on a wide variety of tests that require cerebellar processing. The cerebellum is known to be important for the acquisition of all sensorimotor skills. Its particular contribution to reading is to help control eye movements; but it may also help to mediate the 'inner speech' that is required for phonological analysis—mentally sounding out the letters in a word. It plays an important part in calibrating visual motion signals to help maintain steady eye fixation (Miall, Wolpert and Stein, 1993) and it also calibrates reading eye movements to be precisely adjusted for each saccade from one word to the next and also to control those that take the eyes back to the beginning of each line.

Scott observed that children with cerebellar tumours often present with reading difficulties. The left temporoparietal area projects to the right cerebellum, and both these regions are particularly involved in language related processes. Stoodley, in our laboratory, has confirmed that children with right-sided cerebellar lesions tend to have language and literacy problems, whereas those with left-sided lesions were more likely to have visuospatial problems (Scott *et al.*, in press). In fact, these cerebellar tumours seem to cause more serious and long lasting problems than lesions of the cerebral cortex, whereas if cortical lesions occur early enough most children recover from them almost completely.

We have, therefore, compared the metabolism of the cerebellum in dyslexics with controls' using magnetic resonance spectroscopy (MRS). The cholinein-acetyl aspartate ratio measured by MRS gives an estimate of the metabolic activity of different brain regions. We found that this ratio was lower in the cerebellum of the dyslexics compared with the controls, particularly on the right hand side (Rae *et al.*, 1998). Likewise, in dyslexics it was lower compared with controls in the left temporoparietal region with which the right cerebellum connects. Nicolson *et al.* (1999) then showed that dyslexics have decreased activation of the cerebellum during motor learning. Using positron emission tomography (PET) scanning, they showed that during the acquisition of a five-finger exercise there was very considerably less activation in the cerebellum in dyslexics compared with controls. Thus there is now very little doubt that cerebellar function is mildly disturbed in many dyslexics. Since the cerebellum receives a heavy magnocellular input and itself can be considered the 'head' ganglion of the magnocellular systems, this is further evidence for the hypothesis that impaired magnocellular development underlies dyslexics' problems.

GENETIC BASIS OF POOR TRANSIENT SENSITIVITY

Another exciting implication of the unfolding relationships between reading and physiological sensitivity to sensory transients is that the latter can be measured more objectively, in young children and even in animal models. Hence, the biological basis of these relationships can be explored, starting with their genetic basis.

It is well known that reading problems are strongly hereditary. Twin studies have confirmed this; its heritability (the amount of the variance in reading ability that can be explained by inheritance rather than environment) is *ca.* 60% (Pennington and Smith, 1988; Olson *et al.*, 1989; Pennington, 1991). Although it was initially argued that only phonological ability is inherited, it is now clear that orthographic ability also is highly heritable. Although there is a large common component of the inheritance of both phonological and orthographic skills, in addition unique genetic variance is accounted for by orthographic and phonological skill separately. In other words, at least three genes are probably involved, one controlling linked orthographic and phonological ability, one for orthography alone and one for phonological ability alone.

So far we can be reasonably certain that at least one of the genes controlling both orthographic and phonological ability lies on the short arm of chromosome 6 near the major histocompatibility complex (MHC) Class 1 region. Three groups have now confirmed this association (Cardon *et al.*, 1994; Grigorenko *et al.*, 1997; Fisher *et al.*, 1999), and in our sib pair study we showed that both orthographic and phonological ability link to this site. We have recently completed a genome-wide screen which has shown strong linkages to other sites as well that have not yet been targeted by other studies. These other sites may well show selective linkage to either phonological or orthographic ability as predicted by the unique genetic variance they explain.

IMMUNOLOGICAL MEDIATION?

Many of the putative chromosomal sites linked to reading problems, including of course the MRC site on C6, are involved with immunological regulation. This may be of great significance because of the evidence, most of it still circumstantial, that the impairment in dyslexics' magnocellular development may be mediated by an immunological mechanism. First, developmentally speaking the feature that links all magnocells is their expression of common surface antigens, important for their recognition by other cells (Hockfield and Sur, 1990). Hence they might all be vulnerable to damage at the hands of a rogue autoantibody that recognized that antigen. We now have a small amount of preliminary evidence that mothers may develop antibodies to foetal magnocellular neurones, small quantities of which may under some circumstances cross the placenta and blood brain barrier and damage the developing magnocells (Vincent *et al.*, 2000).

The production of such an antibody would be regulated by the MHC Class 1 system, since one of its most important functions is to distinguish self from not self antigens. Also it seems that this system is pressed into service during development to regulate the differentiation of magnocells (Corriveau and Satz, 1998). In other words, this is probably the system that is responsible for directing the synthesis of antibodies against the foetus. But normally the placenta provides effective protection from them. It seems, however, that vulnerability to such attack may be inherited in dyslexics, because they and their families seem to have more than their fair share of autoimmune diseases such as asthma, hayfever, allergies and more serious autoimmune diseases such as disseminated lupus erythematosus (DLE—Geschwind and Behan, 1984; Hugdahl, Synnevag and Satz, 1990), although this excess incidence has been denied (Gilger *et al.*, 1998).

POLYUNSATURATED FATTY ACIDS

Furthermore, recent reports that many of dyslexics' problems may be exacerbated by modern diets that can contain dangerously low quantities of polyunsaturated fatty acids (PUFAs) can be fitted into this schema. Dyslexia in both children and adults is associated with clinical signs of essential fatty acid deficiency (Richardson *et al.*, 2000; Taylor *et al.*, 2000). As we have seen, magnocellular function is dependent upon the rapid dynamics of their membrane ionic channels. The required conformational changes in channel proteins are facilitated by being surrounded by flexible unsaturated fatty acids. The turnover of these is under the control of phospholipases, in particular PLA2. It has recently been shown that there are increased levels of this enzyme in dyslexics (Macdonnell *et al.*, 2000) which may remove excessive amounts of PUFAs from the membrane and thus compromise rapid channel responses in magnocells. Furthermore, this enzyme may be modulated by the MRC system since immune reactions mobilize PUFAs from cell membranes to provide precursors of the cytokines required for effective cellular responses to foreign material. With the decline of eating fish, modern diets tend to be dangerously low in PUFAs, hence

magnocellular function may be particularly compromised. Therefore supplementing dyslexics' diets with PUFAs may relieve their fatty acid deficiency and help them to learn to read (Richardson *et al.*, 2000).

In summary, therefore, it is possible that the impaired magnocellular function found in dyslexics results from genetically directed antibody attack on their development in the foetus *in utero*, coupled with vulnerability resulting from diets low in essential fatty acids. The different mixes of manifestations of visual/orthographic, auditory/phonological, somaesthetic and/or motor impairments in individual dyslexics would depend on the random chance of which particular magnocells were most affected by these adverse circumstances. This would neatly explain Tim Miles' seminal insight that the manifold expressions of his syndrome in different people are probably connected, and how they are certainly not confined to reading and writing.

THE ADVANTAGES OF DYSLEXIA

However there remains one mystery. The magnocellular defect that I am outlining would definitely be a selective disadvantage, not because of its effect on reading, but because it would undoubtedly be dangerous. Even a mild degree of insensitivity to visual motion would put you at risk of not seeing the advancing sabre toothed tiger quite early enough to avoid death. Not hearing the hiss of the snake might have the same effect, and incoordinated swinging from tree to tree ends up in a mangled heap on the ground below. Accordingly, the allele causing impaired magnocellular development ought to be extremely rare since it should kill off its possessors before they had time to procreate. Only when such a gene carries a compensating advantage, like the sickle cell anaemia gene's protection against malaria, does it survive in the genome; hence the high incidence of magnocellular impairments implies that it may be just one component of a balanced polymorphism that also carries advantages.

Much less is known about these advantages of dyslexia. But in a lecture such as this, I think I am allowed a final section of almost pure speculation. It seems possible that great artistic, inventive, political and entrepreneurial talent may be commoner among dyslexics than might be expected. Their talents are often described as holistic rather than linear; taking in the whole problem or scene statically at once and seeing possible solutions, rather than being confined to the conventional modes of thought that are small scale, sequential in space, time or logic. Certainly there are a great number of very famous, rich and successful people who were probably dyslexic, such as Hans Christian Andersen, Churchill, Eddison, Einstein, Faraday, Rodin, Leonardo da Vinci to name but a few.

Neural development is a highly competitive process with only 10% of the neurones that are generated in the foetus surviving to adulthood. The 'weakest', namely those that prove least useful in signalling and categorizing the environment, are subject to ruthless competition and elimination with only the most successful 10% surviving. Hence the weak magnocellular systems of dyslexics may well result in the emergence of a more efficient

parvocellular system. Visually this may lead to a larger number and stronger connections between parvocells in dyslexics. These advantages to the parvocellular system might explain the holistic talents of dyslexics, because stronger links between distant parvo cells might bind the products of their processing together in a more efficient manner in dyslexic than in ordinary brains. The advantage gained, for instance in being able to accurately memorize your terrain, might well outway the slight disadvantage of poorer motion perception. Hence the reason why dyslexia is so common may actually be that magnocellular weakness may be the necessary sacrifice required to enable the development of strong connectivity between parvocells. These may mediate the parvocellular system's ability to process static, large scale, visual scenes so efficiently. This skill might then extend into cognitive domains to enable the holistic 'lateral thinking' and 'seeing the big picture' that great artists, politicians and entrepreneurs display.

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