Developmental Dyslexia

Early Precursors, Neurobehavioral Markers, and Biological Substrates

edited by

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CHAPTER 3

The Magnocellular Theory of Dyslexia

John Stein

VISUAL REQUIREMENTS OF READING

Eighteen percent of students who exit United States (U.S.) schools are only able to read and write at a level one, a very low level (Fleischman, Hopstock, Pelczar, and Shelley, 2010). This not only consigns such students to risk for later failure, such as very low paying jobs, unemployment, and criminality, but it is also an appalling waste of talent, because in other respects these students are typically within the normal range of intelligence. They fail because reading is very difficult—the most difficult skill that most people ever have to acquire. Reading is difficult because it requires visual analysis of letters and their order, and translation of those letters into sounds. In parallel, it requires learning the phonological structure of a word and learning that continuously spoken words can be split down into phonemes (shorter sounds that may be represented by letters).

Although there is current emphasis on learning phonological skills, the very first step in reading relies on visual analysis of the text. A large proportion of the primary information processing required for reading is visual.

What, more precisely, are the visual requirements of reading? Letters have to be identified correctly; so it is often assumed that the crucial visual process for reading is the system that specializes in object identification. This depends on the small neurons (parvocellular [P] neurons) that constitute 90% of retinal ganglion cells. They signal the fine detail and color of visual targets to the ventral or "what" route that passes from the primary visual cortex toward the visual word form area that is situated in the anterior part of the fusiform gyrus on the under surface of the left occipitotemporal junction (Cohen & Dehaene, 2004).

VISUAL-MAGNOCELLULAR NEURONS

It is equally important to be able to sequence letters in the right order. People with dyslexia are less accurate and slower at sequencing letters than they are at identifying each letter individually. Correct letter sequencing depends on the properties of the other main visual subsystem, the magnocellular (M) system. The M neurons form only 10% of the ganglion cells in the retina, but they are specialized for timing visual events by signaling movement rather than form or color. When the eyes

move, image motion across the retina is an important source of information about the eye movement. The M cells play a crucial part in signaling letter order. They also supply the other forward route from the primary visual cortex the dorsal "where" route, that culminates in the parietal cortex. Here, their main function is to guide visual attention and eye and limb movements (Goodale & Milner, 1992).

M cells project via the magnocellular layers of the lateral geniculate nucleus (LGN) in the thalamus to the primary visual cortex in the back of the occipital lobe and also to the superior colliculus to control eye movements (Maunsell, 1992). The axons of M cells are heavily myelinated so that the signals they project to the visual cortex arrive there approximately 10 ms before the slower ones provided by P cells.

The dendritic fields of M cells are 20 times the size of those of the P cells. As a consequence, at a reading distance of 30 cm, the M cells respond best to large blobs—around 0.5 cm in size (about half the average size of a word). Therefore, M cells cannot identify the shapes of letters, that in small print subtend only about 1 mm, nor detect letter features 0.1 mm in size. Nevertheless, they do rapidly indicate the locations and order of letters so that attention and eye movements can be directed on each in turn. This directs the P system to identify the letters (Cheng, Eysel, & Vidyasagar, 2004). Thus, if the magnocellular system is deficient, focusing attention and fixation of the eyes will be unstable and the process of sequencing letters will be slower and less accurate.

VISUAL SYMPTOMS

Such visual problems are typical complaints by many children with dyslexia who explain that "the letters blur" or "the letters move over each other, so I cannot remember what order they are meant to be in." Many children are so accustomed to letter blur and motion that they do not realize (or report) that it is abnormal unless they are specifically asked. Due to inaccurate focus of attention, many of them fail to gain a clear representation of the order of letters in a word, even without the letters appearing to move around.

Adults with dyslexia rarely complain of unstable vision in the same way. Even in well-compensated adults, the main problem is frequently a difficulty with spelling. Inaccuracies are often regularizations, or phonetic spellings of irregular words, such as "yot" for "yacht." These spelling mistakes reveal the inaccuracies of their memorized visual representations of words and may be visual-attentional in origin, and not simply phonological.

The prevailing opinion among experts is that dyslexic reading problems are mainly phonological, in large part because very few researchers test for visual symptoms as part of a standard diagnostic battery. There is wide-spread agreement that at least some children with dyslexia have visual problems, some experts put its prevalence very low—at less than 10% of all

people with dyslexia (Snowling, 2000). Yet, we find that 50% of the children seen in our U.K. clinics have significant visual problems that are probably due to impaired development of their visual M system (Stein & Fowler, 2005).

MAGNOCELLULAR IMPAIRMENTS IN DYSLEXIA

A search of Pubmed shows that 90% of the studies since 2000 that have sought evidence for such M impairment in people with dyslexia have found it in at least some. Strictly speaking, visual M cells can only be rigorously defined in the subcortical visual system because only in the retina and LGN are they anatomically separated from the P system. Magno and parvo systems converge and interact strongly, so the only way to confirm that deficits in people with dyslexia are confined to the M system is to use stimuli that are selectively processed by the subcortical M neurons in the retina and LGN (Skottun, 2000).

There is strong evidence that people with dyslexia often suffer impaired development of magnocellular cells in the retina and in the LGN. In the retina, the spatial frequency doubling effect indicates the sensitivity of the M ganglion cells (Maddess et al., 1999). People with dyslexia consistently show a higher contrast threshold in this test, confirming their M cell weakness (Pammer & Wheatley, 2001). Livingstone, Rosen, Drislane, and Galaburda (1991) found that the M layers in the LGN in dyslexic brains are selectively impaired. Not only were the cells approximately 25% smaller in the dyslexic as compared to the control brains, but the M cells were not confined to their proper M layers; many had mismigrated into the adjacent konio and parvo layers of the LGN.

The cortical dorsal "where" pathway is also dominated by M input, and abnormalities have been found in people with dyslexia in this pathway as well. Specifically, anomalies have been reported in the primary visual cortex, the prestriate visual motion area (MT/V5), the posterior parietal cortex, and the ultimate goal of both M and P systems, the prefrontal cortex (Rao, Rainer, & Miller, 1997).

Sensitivity to the contrast of black-and-white gratings is mediated mainly by the primary visual cortex (VI). Since Lovegrove's first report (Lovegrove, Bowling, Badcock, & Blackwood, 1980) there have been several studies that have confirmed that the contrast sensitivity (CS) of many people with dyslexia is lower than that of control groups, particularly at the low spatial and high temporal frequencies mediated by the M system (Bednarek & Grabowska, 2002; Cornelissen, Richardson, Mason, Fowler, & Stein, 1995). Other impairments of M function in people with dyslexia involving the primary visual cortex are 1) abnormal temporal gap detection for low contrast and low spatial frequency stimuli (Lovegrove et al., 1980), 2) reduced critical flicker frequency (Chase, 1993), and 3) decreased low spatial frequency contrast sensitivity for flickering and moving stimuli (Edwards et al., 2004; Felmingham & Jakobson, 1995; Mason, Cornelissen, Fowler, & Stein, 1993; Talcott, 1998).

Ninety percent of the visual input to the motion sensitive neurons in the middle temporal visual motion area (V5/MT) is provided by the M system and only 10% comes from other sources. The best way of assessing the sensitivity of these MT neurons in individuals is to measure their responses to visual motion in "random dot kinematograms" (RDKs). Clouds of dots moving in the same direction "coherently" are progressively diluted with noise dots moving in random directions until the subject can no longer detect any coherent motion in the display. This threshold defines motion (visual dorsal stream) sensitivity for each individual. Several researchers have shown that this is reduced in many people with dyslexia (Cornelissen, et al., 1995; Downie, Jakobson, Frisk, & Ushycky, 2003; Hill & Raymond, 2002; Richardson et al., 2000; Samar & Parasnis, 2005; Talcott et al., 2000). Research has also shown reduced velocity discrimination (Demb, Boynton, Best, & Heeger, 1998; Eden et al., 1996) and elevated speed thresholds for motion-defined form (Felmingham & Jakobson, 1995).

People with low motion sensitivity can still be adequate readers (Skoyles & Skottun, 2004). Nevertheless, individual differences in motion sensitivity explain over 25% of the variance in reading ability (Talcott, et al., 2000). In other words, individual dorsal-stream performance—dominated by M cell input—plays an important part in determining how well visual reading skills develop. This observation remains true for everybody, not just those diagnosed with dyslexia.

The posterior parietal cortex (PPC) receives its main visual input from V5/MT. This input plays a crucial role in the PPC function of guiding visual attention, as well as eye and limb movements (Cheng et al., 2004). People with dyslexia have been found to be worse than good readers at cueing visual attention (Facoetti, Turatto, Lorusso, & Mscetti, 2001; Kinsey, Rose, Hansen, Richardson, & Stein, 2004), visual search (Iles, Walsh, & Richardson, 2000; Facoetti, Paganoni, & Lorusso, 2000), visual short-term "retain and compare" memory (Ben-Yehudah, Sackett, Malchi-Ginzberg, & Ahissar, 2001), and attentional grouping in the Ternus test (Cestnick & Coltheart, 1999). These findings show that dorsal stream function is impaired in dyslexia. Of course they do not prove that defects in the M system are entirely responsible, since none of the tests stimulates the peripheral magnocellular system entirely selectively, and the dorsal stream receives 10% of its input from other sources (Skottun, 2001). Nevertheless, as 90% of its input is provided by the M system, M impairment is likely to be the main cause. Moreover, many of the studies mentioned above incorporated control tests for parvo function, such as visual acuity or color discrimination—and dyslexic populations usually proved to be as good or better at these.

Taken together, this evidence suggests that poor dorsal stream performance in people with dyslexia can be mainly attributed to M system weakness, even in the presence of robust parvocellular function (Fukushima, Tanaka, Williams, & Fukushima, 2005; Skoyles & Skottun, 2004).

EYE MOVEMENT CONTROL BY THE DORSAL STREAM

Typically, the dorsal stream not only directs visual attention to a target but also redirects the eyes toward it. Numerous studies have found not only that the direction of visual attention is disturbed in people with dyslexia (Facoetti, Corradi, Ruffino, Gori, & Zorzi, 2010; Vidyasagar, 2004), and also that their eye control during reading is poor (Eden, Stein, Wood, & Wood, 1994; Kirkby, Webster, Blythe, & Liversedge, 2008; Solan, Ficarra, Brannan, & Rucker, 1998). However, it is strongly argued that these abnormalities do not cause reading problems, but are instead the result of not understanding the text. Hence, the reader has to make longer fixations and more reinspections of previous letters to try to decode words (Rayner, 1985). Poor eye control in people with dyslexia has also been demonstrated in several nonreading situations, using tests of fixation stability (Fischer, Hartnegg, & Mokler, 2000) and of smooth pursuit and saccadic control (Crawford & Higham, 2001). These findings imply that poor eye control comes first and may be a significant cause of reading problems.

EVENT-RELATED POTENTIALS

Recording average electroencephalogram (EEG) potentials in response to a moving, low contrast, visual target provides a more objective measure of cortical dorsal stream processing than psychophysical techniques. Of recent visual event-related potential (ERP) studies in people with dyslexia, the great majority have either confirmed Livingstone's (Livingstone et al., 1991) original observation that this population has weaker responses to moving, low contrast targets than do good readers (e.g., Kuba, Szanyi, Gayer, Kremlacek, & Kubova, 2001) or have found that people with dyslexia show slower, smaller, and spatially abnormal visual attentional ERP responses in line with psychophysical results.

AUDITORY TRANSIENT PROCESSING

Although most people do so without thinking, identifying and ordering the sequences of sounds that make up speech is as difficult as sequencing letters visually. All doctors in training know this when they try to distinguish systolic from diastolic heart murmurs. Whether the murmur comes before or after the second heart sound is very difficult to decide for the novice even though these events are far slower than in average speech. Such analysis of sound sequences depends on being able to accurately detect changes in sound frequency and amplitude that are what convey information in speech. Tracking of auditory transients in real-time is mediated by a set of large neurons specialized for rapid temporal processing that may be likened to visual M cells. They contrast with smaller auditory neurons that identify different mixtures of frequencies, such as chords, by their spectral composition. These neurons work less rapidly, like visual P cells.

Thus, it appears that there are auditory equivalents of the visual M and P systems. Likewise, there are analogous dorsal "where" and ventral "what" cortical streams projecting from the primary auditory cortex toward the frontal lobe (Rauschecker & Tian, 2000). However, at no stage are the auditory M and P equivalents entirely separate or anatomically distinct, so they are not normally named M and P as in the visual system.

Paula Tallal was the first to suggest that developmental people with dysphasia and dyslexia may be poor at the auditory temporal processes required for decoding that are mediated by the auditory equivalent of the M pathways (Tallal & Piercy, 1973). Since her suggestion, there have been many hundreds of studies confirming her idea. We found that, whether dyslexic or not, children's sensitivity to changes in sound frequency and amplitude predicted their ability to read nonwords, that is, a test of phonological skill (Snowling, Goulandris, Bowlby, & Howell, 1986). Auditory M sensitivity accounted for nearly 50% of individual differences in phonological skill (Witton, Stein, Stoodley, Rosner, & Talcott, 2002).

As for the visual system, there is a wide difference in opinion of how common it is to find low-level auditory processing problems in people with dyslexia. Estimates range from 10%–70%. Psychophysical tests may not be sensitive enough to reveal the mild deficits that may cause reading problems, so it is still argued that there can be higher level phonological problems without any evidence of lower level auditory temporal processing impairments. However, using a mismatch negativity paradigm, we showed that even in the absence of a psychophysiologically demonstrable deficit, one can usually show some degree of low-level auditory processing impairment that correlates with phonological problems (Stoodley, Hill, Stein, & Bishop, 2006), and Kraus et al., make the same point in Chapter 6. Data regarding deficits in auditory processing in animal models with knock-outs or knock-downs of CDSGs (Fitch & Szalkowski, Chapter 11), as well as electrophysiological data indicating temporal coding inaccuracy in Dcdc2 knock-out mice (LoTurco et al., Chapter 2), further support this notion.

BRAIN-WIDE MAGNOCELLULAR SYSTEMS

In people with dyslexia, poor visual-magnocellular function is often accompanied by poor auditory temporal processing (Talcott et al., 2000). Processing of temporal transients is not confined to the auditory and visual systems. It is a required function throughout the nervous system. People with dyslexia have been shown to have reduced cutaneous and proprioceptive transient sensitivity (Stoodley, Talcott, Carter, Witton, & Stein, 2000) and impaired motor timing mediated by the cerebellum (Nicolson, Fawcett, & Dean, 2001). This combination of deficiencies suggests a common underlying factor. This is likely to be the kind of large neuron

(magnocell) that mediates transient processing functions throughout the nervous system. All such neurons seem to come from the same lineage because they express the same surface recognition molecule to which antibodies such as CAT301 bind. This signature molecule enables them to recognize each other to make useful functional connections (Hockfield & Sur, 1990; Zaremba, Naegele, Barnstable, & Hockfield, 1990).

I have suggested, therefore, that all the features of developmental dyslexia—visual, auditory, linguistic, and motor—may be accounted for by impaired development of CAT301 type magnocellular neurons throughout the brain. The differing degree of expression of this impairment in different systems could explain the large individual differences seen among people with dyslexia—some being mainly visual, others auditory, others uncoordinated, others more purely linguistic.

Shatz and her colleagues have shown that the development of magnocells and their connections, at least in the visual system and the hippocampus, is regulated by the major histocompatibility complex (MHC) cell recognition and immune regulation gene system (Corriveau, Huh, & Shatz, 1998). Most of the 150 MHC genes reside on the short arm of chromosome 6. When M cells start information processing, MHC class 1 proteins begin to be expressed on their surfaces, probably to help them find other M cells with which to interact. If neurons do not make useful connections during development, they are eliminated by the process of apoptosis, summed up in the epithet, "Use it or lose it." Ninety percent of all the neurons generated in the germinal zones are eliminated in this way during the assembly of functional processing networks during development.

The recognition molecules on the neuronal membrane are not only important to identify each and to make effective functional connections, but also to label them as "self" so that microglia scavenging cells do not to attempt to destroy them as foreign invaders. M cells seem to be particularly vulnerable not only to genetic but also to immunological attack and other general environmental damage. Neurons within the M system also seem to be selectively damaged in prematurity, birth hypoxia, malnutrition, autoimmune diseases, and in many overlapping neurodevelopmental conditions, including dyslexia, dyspraxia, dysphasia, dyscalculia, attention-deficit/hyperactivity disorder, autism, bipolar disorder, and schizophrenia (Hari & Renvall, 2001; Stein, 2001). Perhaps the visual, auditory, memory, and motor temporal processing impairments that are seen in dyslexics are all due to underlying abnormal development of this generalized, change to central nervous system–wide, transient processing, magnocellular system.

One can take this idea a step further. Ramus showed in a small group of well-compensated undergraduates with dyslexia that only a few of them had demonstrable auditory, visual, or motor problems, whereas despite their compensation, most could still be shown to have residual phonological difficulties (Ramus et al., 2003). He attributed the latter to a higher level developmental abnormality, perhaps in the angular gyrus

(Ramus, 2004). Because the angular gyrus is an important node in the M–cell dominated dorsal visuomotor stream, clearly this impairment might also involve impaired higher level magnocellular connections.

OPPOSITION TO THE MAGNOCELLULAR THEORY

There has been vigorous opposition to the magnocellular theory (Skottun, 2000). Skottun does not contest that many people with dyslexia suffer a visual deficit, merely that it has not been clearly shown to be dependent upon impaired visual-magnocellular processing. He suggests that the visual deficit can affect both parvocellular and magnocellular systems and that it may be attributed to deficiencies in visual attention. However, since the evidence is now overwhelming that the magnocellular system dominates both bottom-up capture of visual attention and top-down orientation of visual attention that is mediated by the dorsal stream (Cheng et al., 2004), this still leaves the major visual deficit in dyslexia attributable to a magnocellular deficit.

Because there is now general agreement that dyslexia is associated with disordered temporal processing, there has been little opposition to the extension of the magnocellular theory to all kinds of temporal processing that I propose here. Final confirmation or refutation of the general magnocellular theory will only come when the genetic mechanisms controlling the development and specialization of magnocells are fully understood. In the meantime, the evidence will remain tentative and circumstantial. Emergence of insight into complex systems like this is rarely built on just one piece of conclusive evidence. Rather, observations pile on each other until, finally, everyone is convinced one way or the other, and at that point, the field will typically experience a paradigm shift.

GENETICS

Of course, the really interesting question is why people with dyslexia have impaired development of these magnocellular systems. There are three interacting factors that I will consider here: 1) genetic, 2) immunological, and 3) nutritional.

One great advantage of applying genetic techniques to the study of the development of reading skills is that reading is much easier to measure precisely than many other higher functions, such as emotion, motivation, or delusional thinking. Unlike the 600 or so genes of small effect that have been implicated in schizophrenia (Porteous, 2008), only about 10 genes with much larger effects have so far been associated with dyslexia, and their role in reading is steadily being unraveled (Williams & O'Donovan, 2006).

My colleagues and I have capitalized upon the large number of children and families with reading problems that we have seen around Oxford to carry out whole genome quantitative trait linkage (QTL) studies.

We collected nearly 400 Oxford families and replicated many of our findings in 200 Colorado families provided by Richard Olsen. I shall just discuss two new genes that these analyses have revealed.

The first of these is *KIAA0319*, situated on the short arm of chromosome 6 in the middle of the MHC complex (Paracchini et al., 2006). This appears to be under-expressed in dyslexia, and the protein it encodes is now known to be a partly extracellular, surface signature molecule. As described by Lo Turco et al. (Chapter 2), this gene and at least two others are involved in the control of neural migration early in the development of the brain. Unraveling the precise function of these genes promises to revolutionize the understanding of how dyslexia arises and, thereby, the ability to treat it successfully.

AUTOIMMUNITY

The development of M cells is under the control of the MHC gene complex with the gene *KIAA0319* in their midst. One way of identifying M cells throughout the nervous system is to stain them for their characteristic surface antigen with antibodies such as CAT301. Unfortunately, M cells, so vulnerable in other ways, seem also to be particularly vulnerable to antibody attack. Antineuronal antibodies are found in the blood in many general autoimmune conditions such as systemic lupus erythematosus (SLE). The children of mothers with lupus show a very high incidence of dyslexia and other neurodevelopmental conditions (Lahita, 1988). Benasich (2002) found that infants from families with a history of autoimmune disorders display slower auditory processing that affects their language skills. Ectopias similar to those seen in dyslexic brains are found routinely in the brains of BSXB mice, a strain of autoimmune mouse that has been bred as an animal model of lupus (Rosen, Sherman, Emsbo, Mehler, & Galaburda, 1990). It is interesting to note that children with dyslexia and their families consistently report a higher prevalence of immunological problems—not only lupus, which is rare, but also much more common conditions such as eczema, asthma, and allergies (Hugdahl, Synnevag, & Satz, 1990). We found that mothers of children with dyslexia or autism may have circulating antimagnocellular antibodies in their blood (Vincent et al., 2002).

Thus, there appears to be an association between autoimmunity, abnormal magnocellular development, and dyslexia. This provides further support for the hypothesis that magnocellular impairment may underlie the manifold symptoms of dyslexia.

NUTRITION—OMEGA-3 FISH OILS

Another chromosomal site that showed very strong linkage to reading difficulties in our Oxford and Colorado samples of families affected by dyslexia was on chromosome 18 (18p11.2), which is very close to the melanocortin receptor 5 gene (MCR5), even though this receptor is not

strongly expressed in the brain. So far, we do not have any direct evidence as to how this gene may be involved in dyslexia. However, we do know that it is involved in appetite control, in particular affecting the metabolism of omega-3 essential fatty acids. The same site (18p11.2) has been implicated in susceptibility to bipolar depression (Berrettini et al., 1994).

We are particularly interested in a possible role for this gene in the metabolism of omega-3 long chain polyunsaturated fatty acids (LCPUFA) derived from fish oils. A single LCPUFA, the 22 carbon docosahexanoic acid (DHA), makes up 20% of all neuronal membranes; thus, each person has circa 100 g of DHA in his or her brain. It has just the right properties to contribute flexibility and the correct electrostatic profile to the nerve membrane. As such, it has been conserved in eukaryotic membranes throughout evolution since the Cambrian explosion 400 million years ago (Cunnane, Plourde, Stewart, & Crawford, 2007). There are cogent reasons for believing that, because humans evolved near water, their ready access to this molecule from eating fish explains how the human brain came to be so much larger in relation to the rest of the body than is the case in other animals (Horrobin, 2001). DHA seems to be particularly important for proper magnocellular neuronal function because it is "kinky" and thus prevents the lipid molecules in the membrane from packing together too tightly. This confers the flexibility in the membrane that allows ionic channels to open and close very quickly.

However, DHA is continuously removed from membranes by phospholipases because it also forms the basis of many prostaglandin, leukotriene, and interleukin signaling molecules. Likewise, another LCPUFA, eicosapentanoic acid (EPA), is the substrate for eicosanoid prostaglandins, leukotrienes, and resolvins. They all tend to be anti-inflammatory.

Our modern Western diet is dreadful, with too much of the three Ss— salt, sugar, and saturated fat. We also eat far too little oily fish, fat soluble vitamins, and minerals. Hence, a high proportion of the population, particularly from from low socioeconomic households, is dangerously deficient in these essential nutrients. In randomized controlled trials, we were able to show that simply giving deprived children supplement capsules containing EPA and DHA from oily fish, could dramatically improve their visual-magnocellular function, and thereby, their ability to focus attention and improve their reading skills (Richardson & Montgomery, 2005). We also observed that the children we were studying appeared calmer and less aggressive in the playground, perhaps because their magnocellular functions improved. We followed up this finding by giving young offenders in prison supplement capsules containing fish oils, minerals, and vitamins. In a pilot, double-blind, randomized, and controlled trial, we compared active supplements with placebo in more than 250 young men in a tough young offenders institute. The active supplements reduced the prisoner rate of offending by more than one third—"peace on a plate" (Gesch, Hammond, Hampson, Eves, & Crowder, 2002). We

are now completing a much larger study, hopefully to prove conclusively that simply improving these individuals' diets can help them to exercise better self-control and to behave less antisocially. If a simple and cheap solution such as this can powerfully improve magnocellular function, it will have profound implications in society overall.

CONCLUSIONS

The genetic, developmental, nutritional, neuroanatomical, physiological, and psychophysiological evidence that I have reviewed here all support the view that fundamental phonological reading problems in people with dyslexia may be due to mild, but pervasive, impaired development of magnocellular systems throughout the brain. However, definitive proof of this will only come when there is full understanding of how genetic and environmental influences alter the development and later function of these classes of nerve cells.

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