Evidence for a Magnocellular Defect in Developmental Dyslexia

ALBERT GALABURDA AND MARGARET LIVINGSTONE

\( ^c \) Department of Neurology
Beth Israel Hospital
330 Brookline Avenue
Boston, Massachusetts 02215

\( ^d \) Department of Neurology
Children’s Hospital
Boston, Massachusetts 02115

\( ^e \) Department of Neurobiology
Harvard Medical School
Boston, Massachusetts 02115

INTRODUCTION

Developmental dyslexia is the selective impairment of reading skills despite normal intelligence, visual acuity, motivation, and instruction. Several lines of evidence suggest that dyslexic subjects process visual information more slowly than normal subjects. The flicker fusion rate, which is the fastest rate at which a contrast reversal of a stimulus can be seen, is abnormally slow in dyslexic children at low spatial frequencies and low contrasts.\(^1\) Moreover, such visual abnormalities were reported to be found in over 75 percent of the reading-disabled children tested.\(^2\) When two visual stimuli are presented in rapid succession, the two images fuse and appear as a single presentation; the temporal separation necessary to distinguish two presentations measures visual persistence, and this is up to 100 ms longer for dyslexic than for normal children.\(^3-6\) In contrast, dyslexics perform normally on tests having prolonged stimulus presentations.\(^2\)

These perceptual studies suggest that dyslexia affects some part of the visual system that is fast and transient and has high contrast sensitivity and low spatial selectivity. Exactly these properties characterize the magnocellular subdivision of the visual pathway. The primate visual system is composed mainly of two major processing pathways that remain largely segregated and independent throughout the visual system. This subdivision begins in the retina but is most apparent in, and was first discovered in, the lateral geniculate nucleus (LGN), where cells in the ventral, or magnocellular, layers are larger than cells in the dorsal, or parvocellular, layers. The magno and parvo subdivisions differ physiologically in four major ways: magno cells are much more sensitive than parvo cells to luminance contrast,\(^7-9\) they respond faster and more transiently than parvo cells,\(^10-14\) parvo cells are color coded and magno cells are not,\(^10,12,15-17\) and magno cells have slightly lower spatial resolu-

\( ^a \) This work was supported by grants from the National Institutes of Health, the Office of Naval Research, and The Orton Dyslexia Society.

\( ^b \) To whom correspondence should be addressed.
This functional segregation, begun in the retina, is largely maintained throughout the visual system, possibly even up through higher cortical association areas. Therefore a problem selective to the magnocellular pathway could arise at any level from the retina to peristriate visual cortical areas, and it would be difficult, using behavioral tests, to localize the perceptual defects described in dyslexia.

**PHYSIOLOGICAL EVIDENCE FOR A MAGNOCellular DEFECT IN DEVELOPMENTAL DYSLEXIA**

In this study we used physiological rather than perceptual methods to measure the contrast sensitivity and visual temporal resolution of normal and dyslexic adult subjects. The dyslexic subjects (3 males, 2 females; mean age 27.4 ± 3.8 years) all had reading levels well below normal, despite above average intelligence. The control subjects (4 males, 3 females; mean age 25.8 ± 4.5 years) were all normal readers and were matched to the dyslexic subjects in age, intelligence, education, and professional level.

We first recorded averaged visual cortical evoked potentials (VEP) in response to the contrast reversal of a binocularly presented checkerboard pattern at both low and high contrasts (Fig. 1). At 40 percent contrast the VEP looked similar for the two groups. At 4 percent contrast the VEP between 40 and 90 ms differed in the two populations, and, by inspection, this difference could be interpreted as a small broad negative wave being delayed by 20 to 40 ms in the dyslexic sample. In addition, the more distinct large positive wave at around 100 ms was delayed in the dyslexic population. There were differences beyond 150 ms as well, but these were uninterpretable.

Source location studies using multiple electrodes have indicated that the earliest component of the VEP originates in Visual Area 1 (V-1), or in geniculate afferents to V-1, and that the large positive potential peaking around 100 ms (the P100) represents activity in both V-1 and peristriate visual areas. Therefore the earliest abnormalities in the dyslexic VEP suggest that a substantial population of early responding cells in V-1 or geniculate afferents respond abnormally, possibly more slowly, in response to low-contrast stimuli. Since the cellular correlates of the visually evoked potential are poorly understood, we cannot distinguish whether these early differences indicate differences in size or timing of the neuronal responses in the dyslexic population. The slowing of the P100 wave suggests a delay either in an early phase of the peristriate response or a late phase of the V-1 response. We could interpret both the early and the P100 differences as a slowing of the magnocellular response, since the broad negative wave occurring before 50 ms is likely to represent magnocellular activity in V-1, and the P100 is likely to reflect the approximately simultaneous occurrence of parvocellular activity in V-1 and magnocellular activity in subsequent visual areas.

To explore the question of whether the early component of the evoked response in the dyslexics was abnormal in size or simply delayed, we looked at the binocularly evoked response to alternating counterphase contrast reversals of the same checkerboard pattern at several alternation frequencies and contrasts [Fig. 2(a)]. At high contrasts the VEP of all the subjects showed oscillatory responses, phase-locked to the visual stimulus. At lower contrasts the responses of the normal subjects were slightly reduced, but the responses of the dyslexic subjects appeared markedly reduced. We quantified these differences by calculating a Fourier spectrum for each evoked response and measuring the power of the spectrum at twice the stimulating
Cortical evoked responses were recorded from 4 dyslexic and 6 normal subjects. Copper-cup surface electrodes were placed at OZ and at CZ. Stimuli were generated by a Grass Visual Pattern Generator, model 10VPG, on a Grass model VP GM black-and-white monitor with a 60-Hz refresh rate. The stimulus consisted of a 24-cm \times 18.5-cm rectangular checkerboard of 36 rectangles, each 4 \times 3 cm, presented at a viewing distance of 60 cm. (The spatial frequency of the stimulus was thus 0.16 cycles/degree vertically and 0.12 cycles/degree horizontally.) The contrast of the checkerboard was reversed in a counterphase square-wave temporal pattern at 0.5 Hz (1 contrast reversal/second). Responses were recorded and averaged with a Grass Bio-response Averager, model BAI10CD. The signals were amplified 20,000 times and filtered with a low-frequency cutoff of 1 Hz and a high-frequency cutoff of 100 Hz. The light intensity of the monitor was measured with an SIE photometer, and, for all contrasts tested, the luminance averaged over the entire stimulus was 4.0 cd/m². The different contrasts used produced approximately equal increments and decrements around the average luminance. Contrast is expressed as a percentage—\(((L_{\text{max}} - L_{\text{min}})/2(L_{\text{max}} + L_{\text{min}})) \times 100\). For each subject 128 responses, triggered by the stimulus-contrast reversal, were averaged. Then the responses from 6 normal and 4 dyslexic subjects were scanned, digitized, and averaged together. Negative is upward.

frequency (since each cycle of the counterphase reversal pattern consists of two contrast reversals). The results for three contrasts and three stimulating frequencies are shown in Figure 2(b) and (c). At both 2 and 4 percent contrast the dyslexic subjects showed significantly (Mann-Whitney U test, \(p<0.01\)) smaller responses to a 15-Hz stimulus, but their responses to slower stimulation frequencies or to 30 percent contrast at all stimulating frequencies were all within the normal range. This pattern of results is consistent with a selective defect in the magno cellular system.

Cells in the magnocellular system respond well to low-contrast stimuli, and cells in the parvocellular system do not.\(^{5-9,21}\) Therefore the normal responses of the dyslexic subjects to low-contrast stimuli only at the slower stimulation frequencies suggest that the magnocellular system of dyslexics can respond to low-contrast stimuli, but the response is simply slower than normal. The normal responses of the dyslexic subjects to the 15-Hz stimulus at 30 percent contrast could be accounted for by a speeding up of their magno system at high contrasts or to a high-frequency response of the parvo system. We have no way to distinguish between these two possibilities, since in monkeys the magno system does respond more rapidly at high
contrasts than at low contrasts,\textsuperscript{15,16} but the parvo system can also respond to frequencies as fast as 15-Hz stimuli at high contrasts.\textsuperscript{15,16,22}

From our results we draw conclusions similar to those drawn from perceptual experiments—that dyslexic subjects are less sensitive to low-contrast, fast visual stimulation and that the characteristics of the abnormalities are suggestive of a defect in the transient, or magnocellular, subdivision of the visual pathway. Furthermore, because abnormalities in the VEP are evident as early as 50 ms after a visual stimulation, we can say that a defect exists at a very early stage in the magnocellular pathway, at least as early as the input stage of V-1.

\textbf{ANATOMICAL EVIDENCE FOR A MAGNOCELLULAR DEFECT}

\textit{Lateral Geniculate Bodies}

In view of the findings from the evoked-potentials experiments, we examined the brains of 5 dyslexic subjects (4 male, 1 female; mean age 34.2 ± 13.7 years) and 5 nondyslexic subjects (all male; mean age 40 ± 11.2 years). The dyslexic brains came from subjects who were diagnosed in life and had been used in previous anatomical studies.\textsuperscript{23–25} The control subjects had received sufficient testing during life to permit exclusion of the diagnosis of developmental dyslexia. The tissue processing methods have been described before.\textsuperscript{23–26} We used the Yakovlev method for processing whole brains in serial histological sections.\textsuperscript{26} Brains are sectioned at 35 μm, usually every twentieth and twenty-first section is stained for Nissl substance with cresylechtviolet and for myelin by the Loyez method. The section thickness makes the preparations unsuitable for cell counting, but large numbers of unencumbered neurons are available for measuring cell area. Images representing the medial, middle, and lateral portions of parvocellular and magnocellular layers were digitized (512 × 512 × 8) using a GOULD FD-5000 image analysis system interfaced to a DEC VAX 11/750 computer. For each image, a grey-level threshold was selected such that the Nissl-stained neurons were fully filled. Using this threshold, object borders were drawn using an artificial intelligence-based algorithm, after which the investigator selected for measurement every object that was fully isolated from its neighbors and was identifiable by morphology as a neuron.

On inspection of the lateral geniculate nuclei (LGN) the parvocellular layers appeared similar in the two groups, but the magnocellular layers were more disorganized in the dyslexic brains, and the cell bodies appeared generally smaller and more variable in size and shape (Fig. 3). We measured cell bodies in the magnocellular and parvocellular layers of 5 to 9 fields from each LGN. Three independent observers carried out the entire set of measurements. The second and third observers, but not the first, were blind to the identity of the subjects. An average of 320 magnocellular and 740 parvo cells were measured by each observer in each brain. Since there were no systematic regional differences, a single measurement was obtained for each type of neuron, for each brain, for each observer. Across observers both the mean and the median magnocellular areas were significantly smaller in the dyslexic brains \(p < 0.05\) in all cases; Fig. 4. As compared with the control brains, the mean magnocellular area was on average 27 percent smaller in the dyslexic brains. There were no significant differences in the mean parvocellular neuronal areas \(F[1,8] < 1\) in all cases), which also suggests that there are no systematic differences in the degree of tissue shrinkage or staining between the two groups. Two observers found no
normal subject

contrast

2%

5 microvolts

30%

dyslexic subject

msec
FIGURE 2. (a) Cortical evoked responses in two subjects to 15-Hz contrast reversal at two contrasts (2% and 30%) of the same checkerboard pattern as in Figure 1. Negative upward. As indicated at the bottom, the contrast of the checkerboard was reversed in a counterphase square-wave temporal pattern at 15 Hz (30 contrast reversals/second). Each tracing represents the average of 64 sweeps. The bottom tracings indicate the luminance of one square in the checkerboard pattern. (b) and (c) Fourier spectrum analyses of evoked potentials, such as those shown in Figure 2(a), at different contrasts and stimulation frequencies for 7 normal subjects and 5 dyslexic subjects. For each contrast level and stimulus frequency 64 sweeps were averaged, then each response was scanned, digitized, and a Fourier spectrum was calculated. The ordinate indicates the power in the Fourier spectrum at the same frequency as the contrast reversal rate (twice the counterphase reversal rate) of the visual stimulus. Values indicate mean ± SEM. We used a Mann-Whitney U test to determine that the responses of the dyslexic and normal populations differed significantly for 2% and 4% contrast patterns at 15 Hz (p<0.01).
difference in the distribution of cell sizes in the parvo layers, while observer 1 found a greater percentage of larger cells in the dyslexic sample ($\chi^2 = 20.0, df = 8, p < 0.05$).

These results raise the question of whether abnormalities are also present at earlier or later stages in the visual pathway. The magnocellular geniculate layers get their retinal inputs selectively from the large, Type A, retinal ganglion cells, and the parvocellular layers get their inputs from the smaller, Type B, ganglion cells.\textsuperscript{27,28} It would therefore be very interesting to compare retinal ganglion cell size distributions in dyslexic and normal subjects, but the retinas of these subjects were unavailable for study. The Type A ganglion cells have larger diameter axons than the Type B cells,\textsuperscript{27,29} so an abnormality in the large-cell population in the retina might be manifest as a difference in axon diameter distribution at the level of the optic nerves and optic tracts. Tissue prepared for electron microscopy, which is unavailable to us, is needed to measure axon diameter in these structures reliably (c.f. reference 30). Since magnocellular geniculate cells normally have larger diameter axons than parvocellular cells,\textsuperscript{31} we might expect dyslexic brains to show an abnormal axon diameter distribution in the optic radiation, but again, our material did not allow us to make this measurement. The next place we could look for an abnormality in the visual system was V-1. On inspection the overall appearance and lamination of V-1 in the two populations was similar. We wanted to be able to measure some aspect of V-1 that specifically reflected the magnocellular component of the geniculate input. Our first choice would have been to compare the thickness of layer 4Cα, which receives input from the magnocellular geniculate layers, with layer 4Cβ, which receives parvocellular input.\textsuperscript{32,33} Unfortunately these two layers are not clearly distinguishable in either Nissl- or myelin-stained sections. But in the myelin-stained sections we could easily distinguish layer 4B, which receives its input almost entirely from layer
4Ca,34–36 and therefore from the magnocellular geniculate layers indirectly. We compared the thickness of layer 4B to the thickness of layers 2 and 3 together, which receive input predominantly from 4CB.32,33 The ratio of 4B to 2–3 did not differ in the two groups. This particular negative finding does not, of course, rule out other abnormalities in V-1.

The decreased size of the magnocellular geniculate neurons might be expected to have functional consequences and, indeed, the results presented previously suggest that in dyslexic subjects the early stages of the magnocellular subdivision of the visual system process low-contrast information abnormally slowly. Smaller cell bodies would be expected to have thinner axons, and thinner axons would be expected to have slower conduction velocities.37,38 But slower conduction between geniculate and cortex cannot be the sole difference, because a 30 percent decrease in magnocellular axon diameter would result in only about a millisecond delay in geniculo-cortical conduction time, and even a two- or threefold decrease in diameter would result in only a few milliseconds delay. Despite our inability to find other abnormalities in the visual pathway in our material, it is nevertheless quite possible that the magnocellular division of the visual pathway may be affected in dyslexia at many levels. If so, then the processing abnormalities or delays might be cumulative, resulting in observed 20–50-ms delays in the evoked potential and 100–200-ms delays in tasks that require visual discrimination.

ANATOMICAL EVIDENCE FOR DIFFERENCES IN THE AUDITORY SYSTEM

Several workers have suggested that the analysis of fast temporal auditory transitions, critical for language, is specifically handled by the left hemisphere:39–41 In dichotic listening studies rapid acoustic stimuli show left hemisphere dominance, but reduction of the rate of acoustic change diminished lateralization.39 Tallal42,43 has argued convincingly that children with developmental language deficits may suffer from fundamental disturbances in sound perception. Individuals with developmental
reading disorders, too, have been reported to exhibit difficulties with temporal sound processing and sequencing.\textsuperscript{44-46} Tallal and colleagues\textsuperscript{57-60} have suggested that the development of adequate reading competence depends on normal auditory perception. Zinkus \textit{et al.},\textsuperscript{50} Webster \textit{et al.},\textsuperscript{51} and others have reported pervasive language and reading disturbances in children with chronic, severe otitis media. Shucard \textit{et al.},\textsuperscript{52} found amplitude asymmetries of auditory evoked responses that were in opposite directions in dyslexics and controls, and Pinkerton \textit{et al.}\textsuperscript{53} found early and late amplitude and asymmetry differences consistent with a disturbance in both early and late auditory processing in dyslexics, but not all studies have agreed on these findings.\textsuperscript{54,55} A high frequency of spelling errors was found to correlate with low auditory evoked potential amplitudes at P50 and P300 by Byring and Jarvilehto,\textsuperscript{56} and related findings have been reported by others (reference 57; see review by Obrzut \textit{et al.}\textsuperscript{45}).

We examined the medial geniculate nuclei (MGN) in autopsy specimens from the same subjects described in the abovementioned LGN study prepared in the same fashion. Each MGN was thoroughly sampled without regard to nuclear subdivision and 600–700 neurons per brain were drawn using a camera lucida setup under 500x magnification. Measurements were made with a MOP-3 Zeiss planimeter. Sections were coded and randomly right–left reversed so that the morphometrist was not aware of group (dyslexic versus non) or side (right versus left). There was no overall difference in mean area between dyslexic and control MGN neurons, but the difference between cell areas of left dyslexic MGN and left control MGN neurons approached significance. When cells were grouped into bins of 50 or 100 \(\mu\text{m}\), the distribution of neuronal sizes differed between dyslexics and controls, with the dyslexic sample showing a relative paucity of large neurons and a relative excess of small neurons. This was because the left MGN of dyslexics, as compared to controls, showed more small cells and fewer large cells. There was an asymmetry in the proportion of large cells in the direction of the left MGN in the control sample and in the direction of the right MGN in the dyslexic sample.

**DISCUSSION**

Despite many gaps, the picture beginning to emerge from anatomical and physiological studies of the visual system is that the segregation apparent at very early stages gives rise to separate and independent parallel pathways. Physiological studies indicate that the magnocellular system carries information about motion and stereopsis, and perceptual studies suggest that it may be largely responsible for motion perception, spatial localization, depth perception from many kinds of depth cues (stereopsis, perspective, shading, and motion), hyperacuity, figural grouping, illusory border perception, and figure/ground segregation (for references, see reference 58). The parvo system seems to be concerned with color perception, object recognition, and high-resolution form perception. The observations that dyslexics often have poor stereoaucity,\textsuperscript{59} visual instability, and problems in visual localization\textsuperscript{60} are all consistent with a selective deficit in the magnocellular pathway, but as far as we know no one has compared dyslexics and normals for any of the other proposed magnocellular functions.

The role of the magnocellular system in reading is still unknown. Lovegrove \textit{et al.}\textsuperscript{61} have suggested that the transient system rapidly transmits information about spatial organization (for reading this would involve the arrangement and overall shape of words and letters), and then the slower sustained system deciphers the
details (syllables and letters). They have also suggested that an even more important role might be that with each saccade the transient system inhibits the sustained system, erasing the otherwise persistent image of the previous fixation, which is consistent with the prolonged afterimages experienced under conditions of impaired magnocellular activity.59

If the problem in dyslexia is that a slower magnocellular system does not sufficiently precede the information from the parvo system, then manipulations that slow the parvo system more than the magnoc cell system might restore the proper temporal relationship. Indeed, simply reducing the contrast of black letters on a white page by a factor of 2.5, which would be expected to slow processing more in the parvo system than in the magnoc cell system,14-16 has been reported to improve reading performance in reading-disabled children.62 Since diffuse red light, and not white or shorter wavelength light, produces a sustained inhibition of many magnocellular geniculate cells,10 the use of colored filters63,64 may alter the performance of the magnoc cell system.

Orton65 suggested that dyslexia may arise not from high-level cognitive problems, but rather from perceptual deficits. Since then, however, many authors have argued that dyslexia is a specifically linguistic problem arising from a poor understanding of the phonological structure of words.56-69 There may be a link, however, between perceptual processing and phonological capabilities. Language- and reading-impaired children have trouble distinguishing both consonant-vowel phonemes and nonlinguistic cues if they have rapid (around 40 ms) auditory transitions, but they perform normally with other auditory discriminations, both linguistic and nonlinguistic.47,70,71 Studies that test the temporal resolution of the visual system find that most reading-disabled children show defects only in rapid visual information processing, and that these same children do poorly on tests of phonological skills.2,72 Dyslexia and dysphasia (specific developmental language delay) have both been thought to be very high-level, even cognitive, defects, since these children do poorly in some auditory, somatosensory, visual, and motor tasks as well as linguistic tasks. But Tallal et al.73 found that language-impaired children did poorly in each of these modalities only for tasks that required very rapid information processing. Thus defects in rapid information processing may not be limited to the visual modality, and problems in the ability to discriminate rapid auditory transitions may underlie the linguistic problems. The preliminary findings in the MGN previously described may represent the anatomic substrate of the defect in rapid auditory processing seen in dyslexics. Thus, the relative paucity of large cells in the left MGN of dyslexics may prevent the lateralization of rapid processing to the left hemisphere, which is likely to represent an important factor in language lateralization. Normal acquisition of phonological competence may depend on normal auditory perception at critical developmental times.

The linguistic changes may also relate to anatomical findings described in several earlier studies of these same autopsy specimens—anomalous cerebral asymmetry of a language area known as the planum temporale and developmental cortical abnormalities affecting parts of this and other language areas.23-25 The relationship between the previous and present anatomic findings is not known. The anatomy of the cortical language areas may be modified by abnormal early sensory input. In that case, the changes in the language areas of dyslexic brains could reflect abnormal early sensory input. On the other hand, the pathologic factors that disturb the visual and auditory thalamic nuclei may also act directly on the development of the language areas and other cortical areas themselves. Indeed, the language areas of the planum temporale, which are characterized by the presence of large pyramidal
neurons and rich intracortical myelination, may form part of the fast components of the auditory system and could therefore be affected by a disease process that targets fast subsystems.

Other sensory and motor systems are also functionally subdivided, and it is likely that these areas, like the visual system, are segregated into fast and slow subdivisions. This is particularly likely in light of the observations of McGuire et al., who found that an antibody, CAT 301, selectively stains the magnocellular subdivision of the visual pathway, from the geniculate through primary and secondary visual cortices up through higher parietal visual areas; this same antibody stains many other cortical areas, including some, but not all, somatosensory areas, a subset of the motor areas, and many other less well-defined areas. Most of these areas differ from areas that do not stain with CAT 301 in that they are heavily myelinated, suggesting that these areas all have in common the ability to process information rapidly. The neuronal subdivisions involved in fast information processing in each modality thus may share particular molecular entities and might thereby be vulnerable to the same pathogenic factors. We suggest therefore that dyslexics and dysphasics have a specific defect in the rapid subdivisions, the magnocellular homologues, of many forebrain systems.

ACKNOWLEDGMENTS

We thank Rita Burke and Jane McGuiggin for technical help with the evoked potentials. We thank Antis Zalkalns, who processed the human specimens for histology, and William H. Baker, Jr., and The Orton Dyslexia Society, who helped establish access to brain donors for this research project.

REFERENCES