Physiological and anatomical evidence for a magnocellular defect in developmental dyslexia

(visual perception/magnocellular geniculate/parvocellular geniculate)

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ABSTRACT Several behavioral studies have shown that developmental dyslexics do poorly in tests requiring rapid visual processing. In primates fast, low-contrast visual information is carried by the magnocellular subdivision of the visual pathway, and slow, high-contrast information is carried by the parvocellular division. In this study, we found that dyslexic subjects showed diminished visually evoked potentials to rapid, low-contrast stimuli but normal responses to slow or high-contrast stimuli. The abnormalities in the dyslexic subjects' evoked potentials were consistent with a defect in the magnocellular pathway at the level of visual area 1 or earlier. We then compared the lateral geniculate nuclei from five dyslexic brains to five control brains and found abnormalities in the magnocellular, but not the parvocellular, layers. Studies using auditory and somatosensory tests have shown that dyslexics do poorly in these modalities only when the tests require rapid discriminations. We therefore hypothesize that many cortical systems are similarly divided into a fast and a slow subdivision and that dyslexia specifically affects the fast subdivisions.

Developmental dyslexia is the selective impairment of reading skills despite normal intelligence, sensory acuity, motivation, and instruction. Several perceptual studies have suggested 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 >75% 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 msec longer for dyslexic than for normal children, particularly for low spatial frequency stimuli (3–6). Dyslexic subjects also have trouble distinguishing the order of two rapidly flashed visual stimuli (7). In contrast, dyslexics perform normally on tests having prolonged stimulus presentations (2).

These perceptual studies suggest an abnormality in dyslexia affecting 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 (8, 9). 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. In the retina and the LGN, the magnocellular and parvocellular subdivisions differ physiologically in four major ways: color selectivity, contrast sensitivity, temporal resolution, and acuity (8, 9). This functional segregation, begun in the retina, continues throughout the visual system, possibly even up through higher cortical association areas. Therefore a problem specific to the magnocellular pathway could originate at any level from the retina to previsuial cortical areas, and it would be difficult, using behavioral tests, to localize such perceptual defects.

In this study, we used physiological rather than behavioral methods to measure the visual temporal resolution and contrast sensitivity of normal and dyslexic adult subjects, and we have correlated these physiological results with anatomical observations in autopsy specimens.

MATERIALS AND METHODS

A total of five dyslexic and seven normal subjects participated in the visually evoked potential (VEP) studies. Only four dyslexic and six normal subjects were tested with the 0.5-Hz stimulus (transient pattern reversal VEP). The dyslexic subjects (three males and two females; mean age, 27.4 ± 3.8 years) all had been formally diagnosed and were of above average intelligence. The control subjects (four males and three 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. Copper-cup surface electrodes were placed at OZ (90% of the distance from nasion to inion) and at CZ (reference electrode, 50% of the distance from nasion to inion) (10). Stimuli were generated by a Grass visual pattern generator, model 10VPG, on a Grass model VPGM black and white monitor with a 60-Hz refresh rate. The stimulus consisted of a rectangular checkerboard (24 × 18.5 cm) of 36 rectangles (each 4 × 3 cm) presented at a viewing distance of 60 cm. (Spatial frequency was thus 0.16 cycle per degree vertically and 0.12 cycle per degree horizontally.) The contrast of the checkerboard was reversed in a counterphase squarewave temporal pattern at 0.5 Hz (1 contrast reversal per sec) for the transient VEP and at various frequencies for the steady-state VEP. Responses were triggered by the stimulus contrast reversal and recorded and averaged with a Grass Bio-response averager, model BA10CD. The signals were amplified 20,000 times and filtered with a low-frequency cut-off of 1 Hz and a high-frequency cut-off 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

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Abbreviations: VEP, visually evoked potential; LGN, lateral geniculate nucleus.
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4.0 cd/m². Contrast is expressed as a Michelson fraction—
\((L_{\text{max}} - L_{\text{min}})/(L_{\text{max}} + L_{\text{min}})\).

We examined the LGN in autopsy specimens from five
dyslexic subjects (four males and one female; mean age, 34.2
\(\pm\) 13.7 years) and five nondyslexic subjects (all males; mean
age, 40 \(\pm\) 11.2 years). All of the dyslexic brains came from
subjects who were diagnosed in life and had been used in
previous anatomical studies (11, 12). The control subjects had
had sufficient testing during life to permit exclusion of the
diagnosis of developmental dyslexia. We used the Yakovlev
method for processing whole brains in serial histological
sections (13). Brains were sectioned at 35 \(\mu\)m, and every 20th
section was stained for Nissl substance with cresylechviolet.

Images representing the medial, middle, and lateral portions of parvocellular and magnocellular layers were digitized
\((512 \times 512 \times 8)\) using a Gould FD-5000 image analysis system
interfaced to a DEC VAX 11/750 computer. For each image,
the observer selected a gray-level threshold so that most of
the Nissl-stained neurons were fully filled. Using this thresh-
old, object borders were drawn using an artificial intelligence-
based algorithm, and the observer then selected for auto-
mated measurement every isolated object that was fully filled
and was identifiable by morphology as a neuron.

RESULTS

We used physiological methods to compare the contrast
sensitivity and temporal resolution of normal and dyslexic
adult subjects. We recorded visually evoked potentials to the
contrast reversal of a binocularly presented checkerboard
pattern at both low and high contrasts (Fig. 1). At a contrast
of 0.2, the VEP looked similar for the normal and dyslexic
groups. At the lower contrast of 0.02, however, the dyslexics' VEP showed early differences that could be interpreted as a 20-
to 40-msec delay in a small broad negative wave, which
in the normal subjects peaked around 50 msec. The early
phase of the evoked response is quite variable between
subjects and under different stimulus conditions (14) so it is
difficult to interpret the differences we found, but it has been
suggested that the earliest negative wave of the contrast
appearance-evoked potential represents activity in the mag-
nocellular system because it shows high contrast sensitivity
and is maximum at low spatial frequencies (15). In all the
normal subjects we tested, at low contrasts the earliest
component of the VEP was negative-going, and in all the
dyslexic subjects tested this component was missing or
delayed. Although anatomical substrates of the VEP are
poorly understood, the early negative wave of the pattern-
reversal VEP probably reflects activity in thalamo-recipient
layer 4C of visual area 1 (16–18). The dyslexic subjects also
showed a delay in the large positive wave normally peaking
around 100 msec, as well as differences at longer times that
are uninterpretable.

Since differences in transient VEPs are not easily inter-
preted or quantified, we decided to look at steady-state
evoked potentials to rapidly alternating patterns, because the
sinusoidal shape of the wave allows simple measurement of
the amplitude of the response (19). We recorded responses to
alternating counterphase contrast reversals of the same
checkerboard pattern at several frequencies and contrasts
(Fig. 2). At high contrasts, the VEP for all subjects showed
oscillatory responses, phase-locked to the visual stimulus. At
15 Hz the responses of the normal subjects to low-contrast
stimuli were slightly reduced, but the responses of the
dyslexic subjects almost disappeared. Fourier spectra of
these responses (Fig. 3) showed that at contrasts of 0.01 and
0.02 the dyslexic subjects produced significantly smaller
responses to a 15-Hz stimulus \((P < 0.01;\) Mann–Whitney U
test) but normal responses to slower stimulation frequencies
or to higher contrast at all stimulating frequencies. Since cells
in the magnosystem respond well to low-contrast stimuli,
and cells in the parvo system do not (8, 9), this result suggests
that the magnosystem of dyslexics can respond to low-
contrast stimuli, but the response is simply slower than
normal, consistent with the apparent delays in the early
components of the evoked response. The normal responses of
the dyslexic subjects to the 15-Hz stimulus at higher
contrast could be accounted for by a speeding up of their
magnosystem at high contrasts or to a high frequency
response of the parvo system. We have no way to distin-
guish between these two possibilities since in monkeys the
magnosystem does respond more rapidly at high contrasts than
at low contrasts (9, 20), but at high contrasts the parvo system
can also respond to frequencies as fast as 15 Hz (20, 21).

Our VEP results thus suggest an abnormality in the mag-
nocellular pathway at the level of visual area 1 or earlier. We
therefore examined Nissl-stained sections of the LGN from
autopsy material from five dyslexic and five nondyslexic
subjects. On inspection, 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 smaller. A computerized image analysis system
was used to measure cell body area. For three independent
observers (two blind as to the identity of the subjects) both
the mean and median magnocellular areas were significantly
smaller (on average, 27\% smaller) in the dyslexic brains \((P <
0.05\) in all cases, repeated measures analysis of variance;
Table 1 and Fig. 4). There were no significant differences
between controls and dyslexics in the cell sizes in the
parvocellular layers, which excludes any systematic differ-

![Fig. 1. Averaged visually evoked responses from normal and dyslexic subjects. For each subject at each contrast 128 re-
sponses were averaged. Then the responses from six normal and
four dyslexic subjects were scanned and digitized, and the re-
sults for each group were averaged together. Negative is upward.](image-url)
The dyslexic subjects or by contrasts We used then each averaged, for spectrum at grouping, illusory spatial localization, depth information about motion and Physiological the in magnified bodies are slower conduction velocities. are consistent with our physiological findings: smaller cell bodies are likely to have thinner axons, which should have slower conduction velocities. These abnormalities might be magnified if there were also defects at earlier or later stages in the magnocellular pathway.

**DISCUSSION**

Physiological studies indicate that the magno system carries information about motion and stereopsis, and human perceptual studies suggest that it may also be responsible for spatial localization, depth perception, hyperacuity, figural grouping, illusory border perception, and figure/ground segregation (22). The observations that dyslexics often have poor stereoaucity (23), visual instability, and problems in visual localization (24) are consistent with a problem in the magnocellular pathway. Moreover, reading is difficult for normal subjects when the letters and background are different colors but have no luminance contrast, a condition under which the magno system responds very poorly (22, 42).

The role of the magnocellular system in reading is unknown, but it has been suggested (25, 26) that after each saccade the magnocellular system must inhibit the parvocellular system, erasing the otherwise persistent image of the previous fixation. Another possibility, perhaps related, is raised by the finding that the magnocellular system may be essential for maintaining positional stability during saccades (25, 27).

Many authors have argued that dyslexia is a specifically linguistic problem arising from a poor understanding of the

![Picture](image-url)

**Fig. 2.** Examples of cortical evoked responses in two individual subjects, a control and a dyslexic, to 15-Hz contrast reversal of the same checkerboard pattern as in Fig. 1. Negative is upward. As shown in the lower trace, which indicates the luminance of one square in the checkerboard pattern, the contrast of the checkerboard was reversed in a counterphase squarewave temporal pattern at 15 Hz (30 contrast reversals per sec). Each tracing is the average of 64 sweeps. Note that the dyslexic subject shows a much reduced response at a contrast of 0.01.

![Picture](image-url)

**Fig. 3.** Fourier spectrum analyses of evoked potentials, such as those shown in Fig. 2, at different contrasts and stimulation frequencies for seven normal subjects and five dyslexic subjects. For each subject, and for each contrast level and stimulus frequency, 64 sweeps were averaged, then each response was scanned and 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 stimulus cycle rate) of the visual stimulus. Values indicate means ± SEM. We used a Mann–Whitney U test to determine that the responses of the dyslexic and normal populations differed significantly for the two lowest contrasts at 15 Hz (z value for 0.01 contrast = −2.3; z value for 0.02 contrast = −2.6; for both contrasts, P < 0.01). The normal responses of the dyslexic subjects to the 15-Hz stimulus at 0.15 contrast could be accounted for either by a speeding up of their magno system at high contrasts or by a high frequency response of the parvo system, and we cannot distinguish between these possibilities.
phonological structure of words (28–30). Linguistic deficits may, however, be related to perceptual problems since many phonemic discriminations involve rapid auditory transitions, and dyslexic and dysphasic children experience difficulties distinguishing nonlinguistic as well as linguistic auditory stimuli with rapid (~40 msec) auditory transitions, but they perform normally with slower stimuli, both linguistic and nonlinguistic (31-34).

Other cortical systems exhibit functional segregation (35–37), and it is likely that they also have fast and slow subdivisions. This is particularly likely in light of the observations of McGuire et al. (38), who found that an antibody, CAT 301, selectively stains the magnocellular subdivision of the visual pathway, from the LGN 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 they 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 hypothesize that in dyslexics the rapid subdivisions (the magnocellular homologues) of many forebrain systems might be slower than normal. Indeed, in behavioral tests, Tallal et al. (39) have shown that 98% of language-impaired children (children who have trouble learning to speak as well as read) could be differentiated from controls based solely on a battery of tests that require rapid speech production or rapid perceptual discriminations, both somatosensory and auditory.

Earlier studies of these same autopsy specimens (11, 12) reported anomalous cerebral asymmetry of a language area known as the planum temporale and developmental abnormalities of this and other language areas. Normal acquisition of phonological competence may depend on normal auditory perception at critical developmental times, and the anatomy

![Fig. 4. Histological findings in control and dyslexic autopsy brains. The histograms show mean cell areas in the magnocellular and parvocellular layers of dyslexic and control LGN. The data are summed over all observers. * , P < 0.05, for all observers, repeated measures analysis of variance.](image_url)
of the language areas may be modified by abnormal early sensory input (40, 41). On the other hand, the pathologic factors that disturb the magnocellular subdivision of the visual pathway may also act directly on the development of the language areas themselves. Indeed, the language areas of the planum temporale are characterized by the presence of large pyramidal cells and rich myelination and may form part of the fast components of the auditory system.

Informed consent was obtained from all of our subjects after the nature and possible consequences of the study had been fully explained. Antis Zalkins processed the human specimens for histological analysis. Rita Burke and Jane McGuiggin provided technical help with the evoked potentials. William H. Baker, Jr., and the Orton Dyslexia Society helped establish access to brain donors for this project. We also thank an anonymous referee for helpful comments and the Office of Naval Research and the Orton Dyslexia Society for support.

Genetics. In the article “Use of the DNA polymerase chain reaction for homology probing: Isolation of partial cDNA or genomic clones encoding the iron–sulfur protein of succinate dehydrogenase from several species” by Stephen J. Gould, Suresh Subramani, and Immo E. Scheffler, which appeared in number 6, March 1989, of Proc. Natl. Acad. Sci. USA (86, 1934–1938) the partial amino acid sequence reported for the iron–sulfur protein of succinate dehydrogenase from Droso phila melanogaster is in error. The entire gene has recently been cloned (H. Au and I.E.S., unpublished work), using the same partial cDNA clone in the screening of a D. mel anogaster genomic library. There are a significant number of sequence changes (approximately 72% sequence identity with the mammalian coding sequence), which make us believe that the original clone arose from a mix-up or a contamination. The paper described a relatively unusual, at the time, application of the polymerase chain reaction, and it was illustrated by cloning partial genomic or cDNA sequences from several species. The human and Saccharomy ces cerevisiae sequences have since been confirmed independently by us and by others (1, 2).


Biochemistry. In the article “Marek disease virus encodes a basic-leucine zipper gene resembling the fos/jun oncoproteins that is highly expressed in lymphoblastoid tumors” by Dan Jones, Lucy Lee, Juinn-Lin Liu, Hsing-Jien Kung, and Joanne K. Tillotson, which appeared in number 9, May 1, 1992, of Proc. Natl. Acad. Sci. USA (89, 4042–4046), the authors request that the following correction be noted. In the sequence presented in Fig. 2 on p. 4044, a G residue should be inserted after base +1053. This sequence correction does not affect the protein motifs (basic/leucine zipper or proline repeats) reported in the earlier paper. The correct DNA sequence has been deposited in GenBank.

Cell Biology. In the article “Interaction with basement membrane serves to rapidly distinguish growth and differentiation pattern of normal and malignant human breast epithelial cells” by Ole William Petersen, Lone Rønnov-Jessen, Anthony R. Howlett, and Mina Bissell, which appeared in number 19, October 1, 1992, of Proc. Natl. Acad. Sci. USA (89, 9064–9068), the authors request that the following correction be noted. On p. 9065, left column, line 1, μg/ml should be replaced with mg/ml.

Neurobiology. In the article “Physiological and anatomical evidence for a magnocellular defect in developmental dyslexia” by Margaret S. Livingstone, Glenn D. Rosen, Frank W. Drislane, and Albert M. Galaburda, which appeared in number 18, September 15, 1991, of Proc. Natl. Acad. Sci. USA (88, 7943–7947), the authors request that the following correction be noted. On p. 7944, the first sentence of the first paragraph should read as follows: “We examined the LGN in autopsy specimens from five dyslexic subjects (four males and one female; mean age, 34.2 ± 13.7 years) and five nondyslexic subjects (four males and one female; mean age, 40 ± 11.2 years).”

Biochemistry. In the article “Purification and characterization of cytosolic aconitate from beef liver and its relationship to the iron-responsive element binding protein” by Mary Claire Kennedy, Liane Mende-Mueller, George A. Blondin, and Helmut Beinert, which appeared in number 24, December 15, 1992, of Proc. Natl. Acad. Sci. USA (89, 11730–11734), the authors wish that the following correction be noted. In Table 4, entry 6 (amino acid sequence of domain 4), Arg should be below the first Lys (position 732) and not below the second Lys (position 736).