

Neuronal Asymmetries in Primary Visual Cortex of Dyslexic and Nondyslexic Brains

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Dyslexic brains exhibit histologic changes in the magnocellular (magno) cells of the lateral geniculate nucleus, and consistent with these changes, dyslexics demonstrate abnormal visually evoked potentials and brain activation to magno-specific stimuli. The current study was aimed at determining whether these findings were associated with changes in the primary visual cortex with the prediction that magno components of this cortex would be affected. We measured cross-sectional neuronal areas in primary visual cortex (area 17) in dyslexic and nondyslexic autopsy specimens. There was a significant interaction between hemispheres and diagnostic category; ie, nondyslexic brains had larger neurons in the left hemisphere, whereas dyslexic brains had no asymmetry. On the other hand, cell layers associated with magno input from the lateral geniculate nucleus did not show consistent changes in dyslexic brains. Thus, there is a neuronal size asymmetry in favor of the left primary visual cortex in nondyslexics that is absent in dyslexic brains. This is yet another example of anomalous expression of cerebral asymmetry in dyslexia similar to that of the planum temporale, which in our view reflects abnormality in circuits involved in reading.

Jenner AR, Rosen GD, Galaburda AM. Neuronal asymmetries in primary visual cortex of dyslexic and nondyslexic brains. *Ann Neurol* 1999;46:189–196

Developmental dyslexia may be defined as the relatively selective impairment of reading despite normal intelligence, sensory acuity, motivation, and instruction. In the past 20 years much of the research on this subject has focused on language function. In recent years, however, there has been growing interest in exploring more fundamental sensory processing problems, including auditory and visual perception, which in turn may contribute to the well-documented linguistic deficits.^{1–6}

Psychophysical studies have suggested that dyslexics process transient visual stimuli with low-contrast and high-repetition rates (ie, the domain of the magnocellular pathway) more slowly than nondyslexics. The pathway for processing sustained, high-contrast, slow stimuli, the parvocellular pathway, may be spared.^{2,7–13} An anatomical and visual evoked potential (VEP) study provided additional evidence that dyslexics showed a specific defect affecting the magnocellular pathway. Livingstone and colleagues³ found that, whereas the VEPs of dyslexics and nondyslexics were similar for high-contrast conditions, there was a delay in the early wave (from 0 to N100) in the dyslexic response to low-contrast stimuli. This delay is thought to implicate abnormal activity early in the magnocellular visual pathway from the retina up to visual area 1 (V1; also area

17 of Brodmann). Consistent with these results, quantitative analysis has shown that the neurons in the magnocellular layers of the lateral geniculate nucleus (LGN) in dyslexics were, on average, 27% smaller than those of the nondyslexics, but there were no measurable differences in the neurons of the parvocellular layers.

Additional physiological studies have explored the nature of the visual deficit in dyslexics. Several of these studies^{14–17} have measured VEPs using stimuli that are preferentially processed by the magnocellular and parvocellular pathways. Although the specific stimuli differ from that of Livingstone and colleagues,³ both Lehmkuhle and associates¹⁴ and Kubova and co-workers¹⁷ saw a delay in the early components of the VEP in dyslexic individuals. Victor and collaborators¹⁵ and Johannes and colleagues,¹⁶ on the other hand, did not measure any differences in the VEPs of dyslexics to stimuli processed by either the magnocellular or the parvocellular pathway. Victor and collaborators,¹⁵ however, did report an increase in the response variability in subjects with attention-deficit hyperactivity disorder.

Other studies have supported these findings. For instance, dyslexics had slower flicker fusion rates for stimuli that are specific for magnocellular function, but were not abnormal on tests of parvocellular function.¹⁸

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Received Sep 30, 1998, and in revised form Mar 2, 1999. Accepted for publication Mar 5, 1999.

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In a similar manner, Lehmkuhle and associates¹⁴ reported magnocellular dysfunction in dyslexics, although Victor and colleagues¹⁵ and Cornelissen and co-workers¹⁹ failed to do so. Similar psychophysical studies looking at metacontrast masking,²⁰ contrast sensitivity,¹⁹ and flicker sensitivity²¹ have reported specific delays and differences in processing “magnocellular stimuli” by dyslexics. In contrast, other studies do not support the magnocellular deficit hypothesis.^{22,23} These studies fail to show a difference in the dyslexic’s ability to process magnocellular stimuli.

Besides studies looking at low-level visual processing, several studies have expanded the search for visual processing differences at the cortical level. By using psychophysical tasks, Cornelissen and associates¹⁹ found that dyslexics had a decreased ability to detect coherent motion, whereas Felmingham and Jakobson²¹ reported that dyslexics had more difficulty with completing tasks designed to test the function of the dorsal visual stream. Although these two studies only provide circumstantial evidence that the visual deficit extends to the cortical level, a functional magnetic resonance imaging study has provided more concrete evidence.²⁴ Using a visual motion stimulus, Eden and collaborators²⁴ measured the activation of the visual association area MT/V5 in both dyslexic and nondyslexic men, and found that the same stimulus, which produced robust activation of MT/V5 in nondyslexics, failed to activate this area in dyslexics. Demb and colleagues²⁵ also showed reduced activation in MT in addition to primary visual cortex and several extrastriate areas in dyslexics compared with controls. By using whole-scalp neuromagnetic recordings, Vanni and associates²⁶ failed to show any differences in the activation of MT to moving stimuli but did find slightly longer latencies within the dyslexic population. These recent studies provide preliminary evidence that the visual deficits seen in dyslexics may be the result of differences in the processing of visual stimuli at both the cortical and subcortical levels.

The present study was designed to follow up on the LGN findings in dyslexic brains by determining whether dyslexics’ neurons differed in size in the primary visual cortex (area 17), compared with nondyslexics, and if so, whether they affect magnocellular-linked layers differently from parvocellular-linked layers. Layer IV of area 17 receives input from the LGN. Neurons in layer IVC β receive direct input from the parvocellular layers, whereas neurons in layer IVC α receive projections from the magnocellular LGN layers.^{27,28} We hypothesized in dyslexics that neurons receiving inputs from magnocellular LGN layers would show size differences, whereas those receiving projections from the parvocellular LGN layers would not.

Materials and Methods

We examined area 17 in autopsy specimens from 5 dyslexic subjects (4 men and 1 woman; mean age, 34.8 ± 13.6 years) and 5 nondyslexics (4 men and 1 woman; mean age, 39.4 ± 9.2 years). The dyslexics all had a clear diagnosis in life, and the brains had been used in previous anatomical studies of the LGN and medial geniculate nucleus (MGN).^{3,29} The nondyslexic subjects had sufficient educational histories to permit exclusion of the diagnosis of developmental dyslexia. Information about handedness was available on all dyslexic subjects and 4 of the 5 nondyslexic subjects, with 1 known left-handed subject in each group.

We used the method of Yakovlev³⁰ for processing whole brains in serial histological sections. Brains were sectioned coronally at $35 \mu\text{m}$, and every 20th section was stained for Nissl substance with cresyl violet. A section halfway between the caudal end of the splenium of the corpus callosum and the occipital pole was identified in each hemisphere, and a section rostral (five sections away) and one caudal (five sections away) to it were stained. Therefore, there were two stained sections from area 17 in each hemisphere in each specimen. The sections were coded so that the examiner was blind to both the diagnosis and hemisphere of the section during measuring. Within each section the boundaries of area 17 were marked based on the well-known tripartite appearance of layer IV under low-power light microscopy. Within area 17, fields selected for measurement were $77 \mu\text{m}$ wide and extended perpendicularly from the pial surface across all cortical layers. The demarcation of the layers was made based on the density and morphology of the neurons. These measuring boxes were oriented so that they would fall only on straight portions of the visual cortex, thus avoiding crests of gyri and bottoms of sulci. Under $1,250\times$ magnification the outlines of all neuronal perikarya containing a nucleolus were traced using a camera lucida. The outlined cell areas were then measured by using a Macintosh Plus computer (Apple Computer, Cupertino, CA) coupled with a Zeiss MOP-3 electronic planimeter (Carl Zeiss, Inc, Thornwood, CA). Analyses were performed by using analysis of variance.

Results

At low magnification, area 17 showed no obvious qualitative differences in cytoarchitectonic appearance between the dyslexic and the nondyslexic cortex. As expected, neuronal sizes showed significant laminar differences ($F_{6,68} = 93.0$, $p < 0.0001$), both in the dyslexic and nondyslexic specimens. Mean cross-sectional neuronal areas combined over all layers of bilateral visual cortex showed no significant difference between dyslexics and nondyslexics (Tables 1 and 2). However, when the means were computed for the hemispheres separately there was a significant hemisphere-by-diagnosis interaction for all cortical layers combined ($F_{1,8} = 5.70$, $p < 0.05$): Nondyslexics had larger neurons in the left hemisphere (left = $80.48 \pm 3.17 \mu\text{m}^2$, right = $70.44 \pm 2.32 \mu\text{m}^2$), whereas dyslexics had neurons of similar size in both the right and

Table 1. Mean Cell Area (μm^2) and Number of Neurons in Dyslexic and Nondyslexic Visual Cortex

Subject	Layer	Left Hemisphere		Right Hemisphere	
		Mean	No.	Mean	No.
Dyslexics					
ORT-01	II	80.70 \pm 1.75	100	87.06 \pm 1.51	198
	III	76.26 \pm 2.74	82	83.22 \pm 1.65	199
	IV	65.59 \pm 1.48	339	60.15 \pm 0.90	496
	V	80.03 \pm 3.92	52	91.65 \pm 3.92	75
	VI	102.93 \pm 6.02	100	98.23 \pm 3.68	198
	ORT-02	II	82.93 \pm 1.89	137	93.38 \pm 1.99
III		69.78 \pm 2.24	120	83.00 \pm 2.63	88
IV		59.02 \pm 0.96	361	63.73 \pm 1.11	282
V		73.74 \pm 3.03	48	88.70 \pm 5.51	43
VI		95.80 \pm 3.58	137	89.11 \pm 4.01	145
ORT-05		II	70.41 \pm 1.48	152	71.80 \pm 2.08
	III	87.30 \pm 2.69	147	76.82 \pm 2.50	103
	IV	58.28 \pm 1.41	395	57.38 \pm 1.01	372
	V	91.57 \pm 10.80	27	84.59 \pm 3.97	45
	VI	116.98 \pm 9.08	152	87.48 \pm 3.47	121
	ORT-20	II	90.06 \pm 2.13	150	86.92 \pm 2.38
III		93.84 \pm 3.67	108	86.97 \pm 3.36	138
IV		60.77 \pm 1.28	396	64.33 \pm 1.70	391
V		86.28 \pm 4.80	55	79.26 \pm 4.74	55
VI		97.19 \pm 4.11	150	83.00 \pm 2.84	141
ORT-30		II	87.38 \pm 2.10	150	111.13 \pm 2.94
	III	83.33 \pm 2.53	124	93.35 \pm 2.55	124
	IV	62.17 \pm 1.13	408	77.52 \pm 1.50	373
	V	102.08 \pm 6.94	49	106.08 \pm 4.96	69
	VI	105.22 \pm 3.48	150	128.48 \pm 4.19	153
	Nondyslexics				
ORT-7	II	83.60 \pm 2.89	106	76.00 \pm 2.34	113
	III	92.44 \pm 3.91	92	77.71 \pm 2.62	110
	IV	66.93 \pm 1.39	437	59.71 \pm 1.34	422
	V	105.31 \pm 10.36	36	91.16 \pm 4.75	56
	VI	98.80 \pm 4.10	106	92.30 \pm 3.95	113
	ORT-09	II	89.59 \pm 2.60	106	84.43 \pm 2.15
III		110.50 \pm 3.84	121	76.57 \pm 2.49	134
IV		74.63 \pm 1.85	343	60.41 \pm 1.78	322
V		119.93 \pm 13.96	34	83.00 \pm 76.62	32
VI		129.23 \pm 6.80	106	90.15 \pm 5.09	137
ORT-15		II	88.66 \pm 2.72	102	76.72 \pm 1.82
	III	85.26 \pm 3.35	104	77.80 \pm 2.02	139
	IV	70.06 \pm 1.54	362	59.34 \pm 1.11	467
	V	87.25 \pm 6.48	50	77.15 \pm 5.60	59
	VI	102.13 \pm 5.03	102	99.56 \pm 5.27	145
	ORT-18	II	68.83 \pm 1.47	109	70.35 \pm 1.46
III		67.85 \pm 1.30	117	67.25 \pm 1.482	152
IV		57.88 \pm 0.90	414	55.91 \pm 0.65	506
V		83.09 \pm 7.83	30	72.23 \pm 3.11	70
VI		92.36 \pm 3.95	109	93.59 \pm 3.15	162
RPS-01		II	75.14 \pm 1.59	149	75.89 \pm 1.58
	III	77.82 \pm 1.93	155	69.46 \pm 1.73	136
	IV	59.95 \pm 0.77	532	50.29 \pm 0.82	423
	V	76.95 \pm 2.34	69	69.89 \pm 2.67	53
	VI	95.55 \pm 3.05	149	76.99 \pm 2.52	159

the left hemisphere (left = 77.42 \pm 2.86 μm^2 , right = 79.77 \pm 2.89 μm^2 ; Fig 1).

To ascertain whether this hemisphere \times diagnosis interaction was confined to specific layers of the cortex, each cortical layer was analyzed independently.

This analysis showed that the hemisphere \times diagnosis interaction was significant in layers II/III ($F_{1,8} = 6.2$, $p < 0.05$; dyslexic left = 82.28 μm^2 right = 87.76 μm^2 ; nondyslexic left = 84.04 μm^2 , right = 75.29 μm^2), IV ($F_{1,8} = 8.2$, $p < 0.05$; dyslexic left =

Table 2. Mean Cell Area (μm^2) and Number of Neurons in Dyslexic and Nondyslexic Brains in Layer IV of the Visual Cortex

Subject	Layer	Left Hemisphere		Right Hemisphere	
		Mean	No.	Mean	No.
Dyslexics					
ORT-01	IVB	75.97 \pm 3.72	90	64.00 \pm 1.82	142
	IVC β	70.55 \pm 2.39	107	59.60 \pm 1.75	155
	IVC α	55.27 \pm 1.55	142	57.83 \pm 1.20	199
ORT-02	IVB	67.67 \pm 2.35	86	73.47 \pm 2.53	74
	IVC β	58.6 \pm 1.74	121	62.63 \pm 1.89	89
	IVC α	54.51 \pm 1.05	154	58.51 \pm 1.30	116
ORT-05	IVB	64.39 \pm 3.59	113	62.97 \pm 2.43	99
	IVC β	59.53 \pm 2.47	120	55.99 \pm 1.85	110
	IVC α	53.08 \pm 1.37	162	54.92 \pm 1.21	163
ORT-20	IVB	73.92 \pm 3.30	114	82.41 \pm 4.58	113
	IVC β	60.12 \pm 1.98	115	59.96 \pm 2.56	108
	IVC α	52.24 \pm 1.06	167	55.09 \pm 1.28	170
ORT-30	IVB	73.09 \pm 2.91	105	87.31 \pm 3.99	107
	IVC β	59.40 \pm 1.64	135	73.23 \pm 1.91	129
	IVC α	57.58 \pm 1.36	168	73.90 \pm 1.72	137
Nondyslexics					
ORT-07	IVB	78.11 \pm 3.11	113	71.09 \pm 4.10	103
	IVC β	72.07 \pm 2.92	125	60.50 \pm 2.03	140
	IVC α	57.37 \pm 1.38	199	52.06 \pm 1.04	179
ORT-09	IVB	81.17 \pm 4.43	96	67.91 \pm 4.20	102
	IVC β	77.52 \pm 3.35	91	58.96 \pm 3.70	80
	IVC α	68.92 \pm 2.24	156	55.78 \pm 1.62	140
ORT-15	IVB	74.51 \pm 3.37	118	62.83 \pm 2.33	139
	IVC β	72.66 \pm 2.78	96	61.21 \pm 2.11	134
	IVC α	64.84 \pm 1.88	148	55.55 \pm 1.45	194
ORT-18	IVB	62.071 \pm 2.02	129	60.00 \pm 1.51	135
	IVC β	57.051 \pm 1.53	134	54.63 \pm 1.09	164
	IVC α	54.09 \pm 1.04	151	54.26 \pm 0.88	207
RPS-01	IVB	58.15 \pm 1.68	164	55.30 \pm 1.89	134
	IVC β	53.67 \pm 1.23	168	48.68 \pm 1.23	130
	IVC α	53.38 \pm 1.10	200	47.39 \pm 1.05	159

57.56 μm^2 , right = 60.96 μm^2 ; nondyslexic left = 62.45 μm^2 , right = 54.59 μm^2), and V ($F_{1,8} = 7.32$, $p < 0.05$; dyslexic left = 86.74 μm^2 , right = 90.06 μm^2 ; nondyslexic left = 94.51 μm^2 , right = 78.69 μm^2), but not for layer VI. The layer IV analysis was further extended to sublayers IVB, IVC α , and IVC β . The results showed that the interaction held for IVC β ($F_{1,8} = 12.13$, $p < 0.01$; dyslexic left = 54.53 μm^2 , right = 60.05 μm^2 ; nondyslexic left = 59.72 μm^2 , right = 53.01 μm^2 ; Figs 2 and 3).

The above interaction effect shows that the dyslexics and nondyslexics differ with respect to each other in cross-sectional neuronal area between the two hemispheres. Further analyses were performed to determine whether there were significant asymmetries within both populations. Whereas nondyslexic brains showed significant interhemispheric differences in neuronal sizes over all layers combined (left larger than right; $F_{1,24} = 8.381$, $p < 0.05$), there were no such differences in the dyslexic brains, either over all layers combined or layer by layer. Interhemispheric differences in nondyslexics were significant in layers IV and V ($F_{1,4} = 11.523$,

$p < 0.05$; $F_{1,4} = 8.598$, $p < 0.05$, respectively; see Fig 2). Further analysis for hemispheric asymmetries in sublayers IVB, IVC α , and IVC β in nondyslexic and dyslexic brains showed significant asymmetries in all sublayers in the nondyslexics ($F_{1,4} = 11.119$, $F_{1,4} = 12.737$, $F_{1,4} = 9.185$; $p < 0.05$, respectively); but not in the dyslexics (see Fig 3).

To establish whether the lack of asymmetry in the dyslexics was caused by changes in the left or the right hemisphere, direct comparisons of the hemispheres were made across diagnosis. Neuronal sizes in the left hemisphere of the dyslexics were not significantly different from those of nondyslexics ($F_{1,8} = 0.339$, NS), nor were there significant differences between the right hemispheres ($F_{1,8} = 3.73$, NS) despite a sizable mean difference (dyslexic = 79.8 μm^2 , nondyslexic = 70.4 μm^2).

A mean asymmetry coefficient was calculated for cell sizes for each individual brain by using the following formula: $\text{Right} - \text{Left} / [0.5(\text{Right} + \text{Left})]$. This coefficient was then used in an analysis of variance to compare the dyslexic and nondyslexic groups for extent of

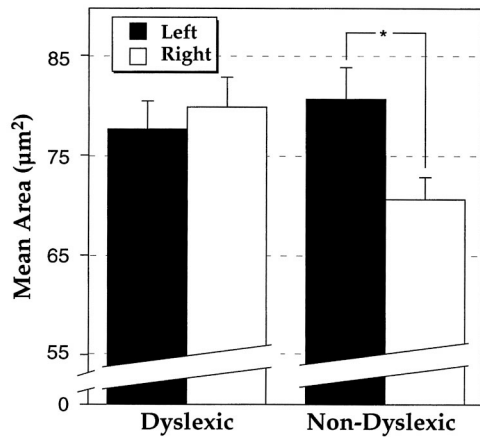


Fig 1. Mean neuronal cell area differs in nondyslexic and dyslexic autopsy brains in area 17. The histograms depict the interaction between diagnosis and hemisphere, revealing an asymmetry in nondyslexics but not in dyslexics (* $p < 0.05$).

asymmetry. As predicted from the mean cell area comparisons, nondyslexics were significantly more biased to the left hemisphere than dyslexics ($F_{1,8} = 5.6$, $p < 0.05$) over all cortical layers combined. Layer-by-layer comparisons of the coefficients of asymmetry revealed that nondyslexics were biased to the left hemisphere in layer IV ($F_{1,8} = 10.2$, $p < 0.05$) and V ($F_{1,8} = 8.5$, $p < 0.05$) and within layer IV, they were asymmetric in IVC α ($F_{1,8} = 14.9$, $p < 0.005$). They were not asymmetric in layers II/III and VI.

Discussion

Anatomical studies have revealed that the magnocellular layers of the LGN project to layer IVC α of the primary visual cortex whereas the parvocellular layers project to layer IVC β .^{27,28} In dyslexics, the neurons of the magnocellular layers of LGN are smaller than in nondyslexics.³ Assuming a developmental interaction between magnocellular neurons in the LGN and those of the primary visual cortex, we postulated that neurons in cortical layer IVC α would be smaller too, perhaps as a result of diminished input from these thalamic neurons. In fact, we did not find this to be the case. The fair degree of blending of the two visual pathways in the cortex, including the primary visual cortex, may explain the lack of specific effects in the magnocellular thalamic projection layers.³¹ Furthermore, the primary visual cortex is under the effect of projection from areas both upstream (the thalamus) and downstream (temporal, parietal, preoccipital, and frontal cortical areas). The further blending of magnocellular and parvocellular systems downstream from the primary visual cortex could obviate the developmental influences from the thalamus. The cross-sectional area

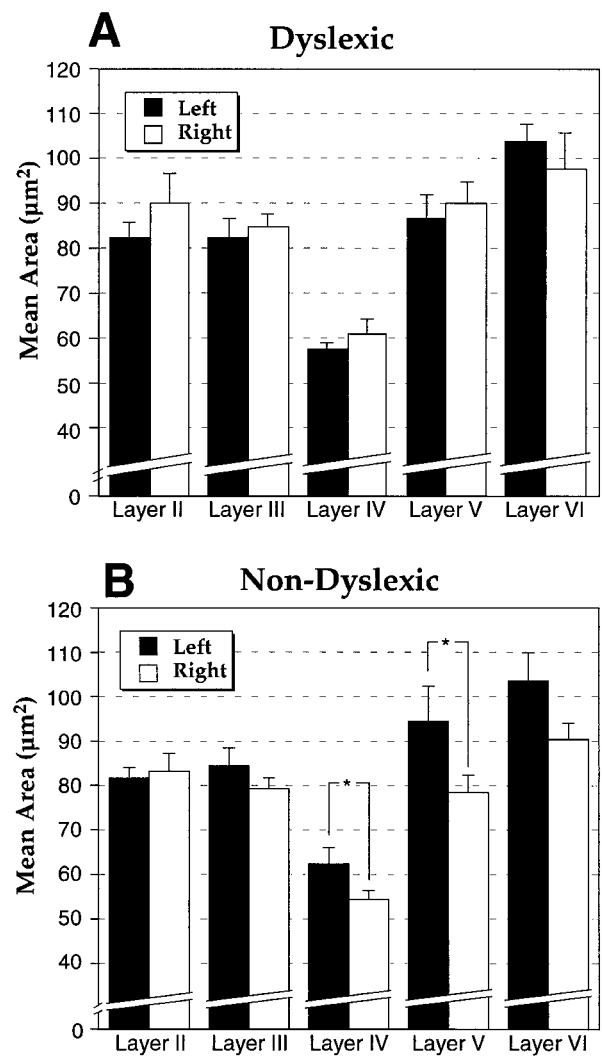


Fig 2. These histograms show the asymmetry in the nondyslexic and the lack of asymmetry in dyslexic for each of the cortical layers (* $p < 0.05$).

of neurons in area 17 did differ between the dyslexics and nondyslexics. Hemispheric asymmetries in the size of neurons over all layers combined, in layers IV and V and in sublayers IVB, IVC α , and IVC β were seen in nondyslexic brains, but not dyslexic brains. A lack of asymmetry has been noted in previous studies of dyslexics.^{32–35} The symmetry of the size of neurons in area 17 is yet another example of symmetry in cortical regions in the dyslexic population.

Although anatomical evidence for laterality in the visual system has not been shown before, many have suggested that there exists hemispheric specialization for some complex visual perceptual tasks. For instance, in a review, Christman³⁶ described a left hemisphere bias for high spatial frequencies in contrast to a right bias for low spatial frequencies.^{37,38} Others have suggested that the visuospatial capacity of the left hemisphere is

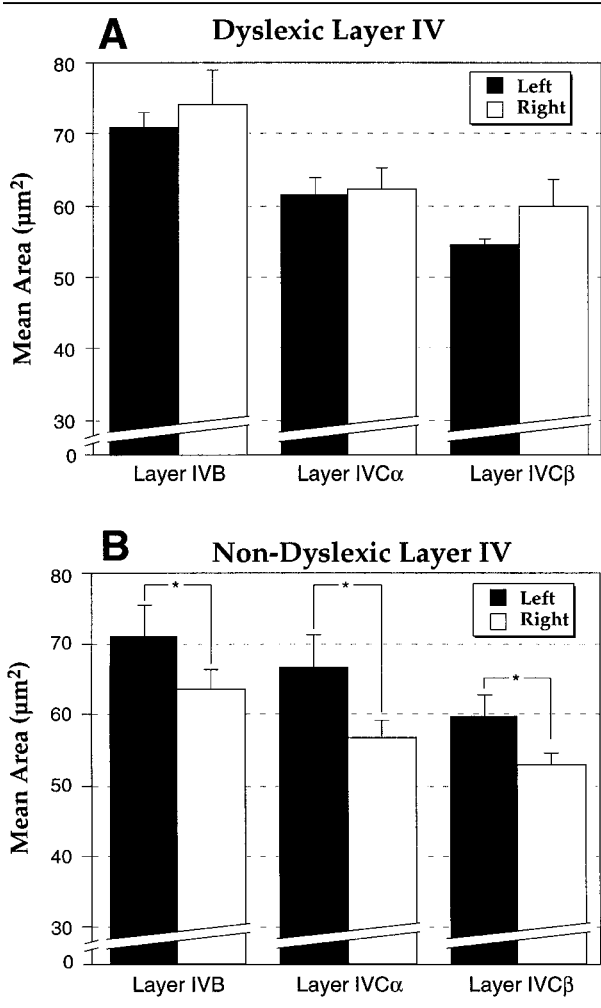


Fig 3. These histograms show the asymmetry in the nondyslexic and the lack of asymmetry in dyslexic for the three sublayers of layer IV (* $p < 0.05$).

categorical, whereas that of the right is metric.^{39,40} Clinical findings in patients with lateralized brain lesions affecting visually related areas appear to support this dichotomy.⁴¹ The asymmetry in the size of neurons in the visual cortex reported here may reflect an anatomical basis for hemispheric specializations others have reported for complex visual perceptual tasks. The lack of asymmetry in the dyslexic population may be contributing to the known visual perceptual differences measured in dyslexics.^{2,3,14,17-21,23,43,44} Additional perceptual tests may reveal more specific differences in some of these complex tasks that are known to be lateralized.

The possibility must also be considered that the differences in asymmetry between dyslexics and controls may result from their differences in reading experience. It is well known that early experience can affect the visual system.^{45,46} The current experiment cannot distinguish whether the reading deficits cause changes in

the asymmetry of neuronal size in the visual cortex, or whether these neuronal differences impact the reading difficulties, or perhaps some as yet unknown interactive effect between the neuronal size asymmetry and reading.

The absence of propagation of size effects from the LGN to the primary visual cortex in dyslexics is at first puzzling. We have already suggested that this may be in part the result of blending of both pathways in visual cortical areas, including area 17, or developmental or functional effects acting top-down from downstream connected cortical areas. The top-down hypothesis may be cited to explain the findings regarding asymmetry and lack thereof. We know that other cortical areas are more symmetric in dyslexic brains,^{32,35,47-49} and symmetry in these other areas of the cortex may propagate top-down to the neurons of the primary visual cortex. On the other hand, there is no reason to exclude the possibility that downstream areas are symmetric because of bottom-up developmental effects from the primary cortex. Furthermore, rather than LGN neurons causing changes in area 17 neurons, the opposite may be true. As stated above, we have shown that symmetry of cortical areas is associated with increased numbers and distribution of interhemispheric callosal projections.⁵⁰ Because there is a normally occurring competition for cortical targets between thalamic neurons and transcallosal neurons,⁵¹⁻⁵⁵ it is possible that with increased symmetry, as seen in the dyslexic brain, and greater numbers of transcallosal neurons, thalamic neurons are deprived of targets resulting in smaller neurons. In all of these cases, it appears likely that the visual system of dyslexics is built or functions differently by virtue of the reported anomalies.

The cause of symmetric development of cortical areas in dyslexic brains is not known. Genetic factors may play a role, as they appear to do for other manifestations of brain laterality.^{56,57} However, we have also shown that the induction of abnormal neuronal migration leading to minor cortical malformations in rats is associated with anomalies of anatomical brain lateralization⁵⁸ and callosal and thalamic connectivity.⁵⁹ In addition, studies of the New Zealand Black mouse, which spontaneously develops ectopias that resemble those seen in dyslexics, have revealed ectopias as early as embryonic day 14 to 15, suggesting that they occur in the middle of the neurons' migrational period.⁶⁰⁻⁶⁵ Tracer studies have shown that these ectopias make anomalous connections to both thalamic nuclei and cortical regions.^{66,67} It is possible, therefore, that the first developmental event in dyslexia is the appearance of such cortical anomalies, which alter the development of cortical asymmetry and of cell sizes in connectionally related cortical and subcortical regions via anomalous connections.

Lack of asymmetry in the cross-sectional neuronal areas of the primary visual cortex of dyslexic brains is

interesting in and of itself, and so is the presence of such asymmetries in nondyslexic brains. Psychophysical and neuropsychological experiments can be used to test whether these anatomical asymmetries may underlie sensory-perception ability and whether the abnormal lateralization in dyslexics may result in abnormal visual perception.

Finally, although this report concentrates on findings in the visual system of dyslexics, related work from our laboratory has shown that the auditory system, too, is anomalous in this population, and that similar fast systems may be preferentially affected.²⁹ By focusing on the visual system of dyslexics, we do not mean to imply that the anomalies reported here and elsewhere in this system are causally related to the reading problem. It is well documented that dyslexics fail in metalinguistic (metaphonological) tasks that require them to break words down into their component phonemes and other similar tasks.⁶⁸⁻⁷⁰ This clearly indicates some problem between language and other cognitive systems, implicating particularly auditory language. We anticipate that neuronal analysis in the primary auditory cortex will also show anomalies in dyslexic brains.

This study was supported in part by PHS grant HD 20806 and the Sackler Scholarship.

We thank Dr G. F. Sherman for his helpful comments on this manuscript and Dr M. Livingstone for her comments and assistance. Acknowledgements also go to Lisa Garcia and Antis Zalkalns for technical assistance.

References

- Tallal P, Piercy M. Developmental aphasia: the perception of brief vowels and extended stop consonants. *Neuropsychologia* 1975;13:69-74
- Martin F, Lovegrove W. Flicker contrast sensitivity in normal and specifically disabled readers. *Perception* 1987;16:215-221
- Livingstone M, Rosen G, Drislane F, et al. Physiological and anatomical evidence for a magnocellular defect in developmental dyslexia. *Proc Natl Acad Sci USA* 1991;88:7943-7947
- Merzenich MM, Jenkins WM, Johnston P, et al. Temporal processing deficits of language-learning impaired children ameliorated by training. *Science* 1996;271:77-80
- Tallal P, Miller SL, Bedi G, et al. Language comprehension in language-learning impaired children improved with acoustically modified speech. *Science* 1996;271:81-84
- Wright BA, Lombardino LJ, King WM, et al. Deficits in auditory temporal and spectral resolution in language-impaired children. *Nature* 1997;387:176-178
- Lovegrove W, Brown C. Development of information processing in normal and disabled readers. *Percept Mot Skills* 1978;46:1047-1054
- Lovegrove W, Heddle M, Slaghuis W. Reading disability: spatial frequency specific deficits in visual information storage. *Neuropsychologia* 1980;18:111-115
- Lovegrove W, Martin F, Slaghuis W. A theoretical and experimental base for a visual deficit in specific reading disability. *Cogn Neuropsychol* 1986;3:225-267
- Lovegrove W, Slaghuis W, Bowling A, et al. Spatial frequency processing and the prediction of reading ability: a preliminary investigation. *Perception Psychophys* 1986;40:440-444
- Lovegrove W, Garzia R, Nicholson S. Experimental evidence for a transient system deficit in specific reading disability. *J Am Optom Assoc* 1990;2:137-146
- Lovegrove WJ. Is the question of the role of visual deficits as a cause of reading disabilities a closed one? Comments on Hulme. *Cogn Neuropsychol* 1991;8:435-441
- May JG, Lovegrove WJ, Martin F, et al. Pattern-elicited visual evoked potentials in good and poor readers. *Clin Vis Sci* 1991;6:131-136
- Lehmkuhle S, Garzia RP, Turner L, et al. A defective visual pathway in children with reading disability. *N Engl J Med* 1993;328:989-996
- Victor JD, Conte MM, Burton L, et al. Visual evoked potentials in dyslexics and normals: failure to find a difference in transient or steady-state responses. *Vis Neurosci* 1993;10:939-946
- Johannes S, Kussmaul CL, Munte TF, et al. Developmental dyslexia: passive visual stimulation provides no evidence for a magnocellular processing defect. *Neuropsychologia* 1996;34:1123-1127
- Kubova Z, Kuba M, Peregrin J, et al. Visual evoked potential evidence for magnocellular system deficit in dyslexia. *Physiol Res* 1996;44:87-89
- Chase C, Jenner A. Magnocellular visual deficits affect temporal processing of dyslexics. In: Tallal P, Galaburda AM, Llinás RR, et al, eds. *Temporal information processing in the nervous system, with special reference to dyslexia and dysphasia*. New York: New York Academy of Sciences, 1993:326-329
- Cornelissen P, Richardson A, Mason A, et al. Contrast sensitivity and coherent motion detection measured at photopic luminance levels in dyslexics and controls. *Vis Res* 1995;35:1483-1494
- Edwards VT, Hogben JH, Clark CD, et al. Effects of a red background on magnocellular functioning in average and specifically disabled readers. *Vis Res* 1996;36:1037-1045
- Felmingham KL, Jakobson LS. Visual and visuomotor performance in dyslexic children. *Exp Brain Res* 1995;106:467-474
- Gross-Glenn K, Rothenberg S. Evidence for deficit in interhemispheric transfer of information in dyslexic boys. *Int J Neurosci* 1985;24:23-35
- Spinelli D, Angelelli P, De Luca M, et al. Developmental surface dyslexia is not associated with deficits in the transient visual system. *Neuroreport* 1997;8:1807-1812
- Eden GF, Vanmeter JW, Rumsey JM, et al. Abnormal processing of visual motion in dyslexia revealed by functional brain imaging. *Nature* 1996;382:66-69
- Demb JB, Boynton GM, Heeger DJ. Functional magnetic resonance imaging of early visual pathways in dyslexia. *J Neurosci* 1998;18:6939-6951
- Vanni S, Uusitalo MA, Kiesila P, et al. Visual motion activates V5 in dyslexics. *Neuroreport* 1997;8:1939-1942
- Livingstone MS, Hubel DH. Connections between layer 4B of area 17 and thick cytochrome oxidase stripes of area 18 in the squirrel monkey. *J Neurosci* 1987;7:3371-3377
- Bassi C, Lehmkuhle S. Clinical implications of parallel visual pathways. *J Am Optom Assoc* 1990;61:98-110
- Galaburda AM, Menard MT, Rosen GD. Evidence for aberrant auditory anatomy in developmental dyslexia. *Proc Natl Acad Sci USA* 1994;91:8010-8013
- Yakovlev PI. Whole-brain serial sections. In: Tedeschi CG, ed. *Neuropathology: methods, diagnosis*. Boston: Little, Brown, 1970:371-378
- Lachica EA, Beck PD, Casagrande VA. Parallel pathways in macaque monkey striate cortex: anatomically defined columns in layer-III. *Proc Natl Acad Sci USA* 1992;89:3566-3570

32. Galaburda AM, Kemper TL. Cytoarchitectonic abnormalities in developmental dyslexia: a case study. *Ann Neurol* 1979;6:94–100
33. Galaburda AM, Signoret J-L, Ronthal M. Left posterior angiomatic anomaly and developmental dyslexia: report of five cases. *Neurology* 1985;25:198 (Abstract)
34. Galaburda AM, Habib M. Cerebral dominance: biological associations and pathology. *Disc Neurosci* 1987;4:1–51
35. Humphreys P, Kaufmann WE, Galaburda AM. Developmental dyslexia in women: neuropathological findings in three cases. *Ann Neurol* 1990;28:727–738
36. Christman S. Perceptual characteristics in visual laterality research. *Brain Cogn* 1989;11:238–257
37. Christman S. Effects of perceptual quality on hemispheric asymmetries in visible persistence. *Perception Psychophys* 1987;41:367–374
38. Sergent J. The effect of sensory limitations on hemispheric processing. *Can J Psychol* 1983;37:345–366
39. VanKleeck M, Kosslyn S. Gestalt laws of perceptual organization in an embedded figures task: evidence for hemispheric specialization. *Neuropsychologia* 1989;27:1179–1186
40. Kosslyn SM, Chabris CF, Marsolek CJ. Categorical vs coordinate spatial relations: computational analyses and computer simulations. *J Exp Psychol* 1992;18:562–577
41. Mehta Z, Newcombe F. A role for the left hemisphere in spatial processing. *Cortex* 1991;27:153–167
42. Borsting E, Ridder WH, Dudeck K, et al. Visual processing in adult dysidetic dyslexics. 1993
43. Borsting E, Ridder WH, Dudeck K, et al. The presence of a magnocellular defect depends on the type of dyslexia. *Vis Res* 1996;36:1047–1053
44. Ridder WH, Borsting E, Cooper M, et al. Not all dyslexics are created equal. *Optom Vis Sci* 1997;74:99–104
45. Hubel DH. The visual cortex of normal and deprived monkeys. *Am Sci* 1979;67:532–543
46. Rakic P, Suner I, Williams RW. A novel cytoarchitectonic area induced experimentally within the primate visual cortex. *Proc Natl Acad Sci USA* 1991;88:2083–2087
47. Galaburda AM, Sherman GF, Rosen GD, et al. Developmental dyslexia: four consecutive cases with cortical anomalies. *Ann Neurol* 1985;18:222–233
48. Larsen J, Høein T, Lundberg I, et al. MRI evaluation of the size and symmetry of the planum temporale in adolescents with developmental dyslexia. *Brain Lang* 1990;39:289–301
49. Leonard CM, Voeller KS, Lombardino LJ, et al. Anomalous cerebral structure in dyslexia revealed with magnetic resonance imaging. *Arch Neurol* 1993;50:461–469
50. Rosen GD, Sherman GF, Galaburda AM. Interhemispheric connections differ between symmetrical and asymmetrical brain regions. *Neuroscience* 1989;33:525–533
51. Ivy GO, Akers RM, Killackey HP. Differential distribution of callosal projections in the neonatal and adult rat. *Brain Res* 1979;173:532–537
52. Ivy GO, Killackey HP. The ontogeny of the distribution of callosal projection neurons in the rat parietal cortex. *J Comp Neurol* 1981;195:367–389
53. Innocenti GM, Clarke S. The organization of immature callosal connections. *J Comp Neurol* 1984;230:287–309
54. Finlay BL, Sengelaub DR, Berian CA. Control of cell number in the developing visual system. I. Effects of monocular enucleation. *Dev Brain Res* 1986;28:1–10
55. O'Leary D, Stanfield B. Selective elimination of axons extended by developing cortical neurons is dependent on regional locale: experiments utilizing fetal cortical transplants. *J Neurosci* 1989;9:2230–2246
56. Annett M. Genetic and nongenetic influences on handedness. *Behav Genet* 1978;8:227–249
57. Annett M. A single gene explanation of right and left handedness and brainedness. Coventry, England: Lanchester Polytechnic, 1978:20
58. Rosen GD, Sherman GF, Mehler C, et al. The effect of developmental neuropathology on neocortical asymmetry in New Zealand Black mice. *Int J Neurosci* 1989;45:247–254
59. Rosen GD, Galaburda AM, Sherman GF. Cerebrocortical microdysgenesis with anomalous callosal connections: a case study in the rat. *Int J Neurosci* 1989;47:237–247
60. Sherman GF, Stone J, Rosen GD, et al. Neuropeptide architectonics in the brain of the New Zealand Black mouse. *Soc Neurosci Abstr* 1987;13:1601 (Abstract)
61. Sherman GF, Rosen GD, Galaburda AM. Neocortical anomalies in autoimmune mice: a model for the developmental neuropathology seen in the dyslexic brain. *Drug Dev Res* 1988;15:307–314
62. Sherman GF, Press DM, Rosen GD, et al. Radial glial immunoreactive fibers in the region of spontaneous microdysgenesis in newborn New Zealand Black mice. *Soc Neurosci Abstr* 1990;16:1152 (Abstract)
63. Sherman GF, Morrison L, Rosen GD, et al. Brain abnormalities in immune defective mice. *Brain Res* 1990;532:25–33
64. Sherman GF, Stone JS, Rosen GD, et al. Neocortical VIP neurons are increased in the hemisphere containing focal cerebrocortical microdysgenesis in New Zealand Black Mice. *Brain Res* 1990;532:232–236
65. Sherman GF, Rosen GD, Stone LV, et al. The organization of radial glial fibers in spontaneous neocortical ectopias of newborn New-Zealand Black mice. *Dev Brain Res* 1992;67:279–283
66. Jenner AR, Galaburda AM, Sherman GF. Connectivity of cortical ectopias in autoimmune mice. *Soc Neurosci Abstr* 1995;21:1712 (Abstract)
67. Jenner AR, Galaburda AM, Sherman GF. Thalamocortical and corticothalamic connections in New Zealand Black mice. *Soc Neurosci Abstr* 1997;27:1365 (Abstract)
68. Swan D, Goswami U. Phonological awareness deficits in developmental dyslexia and the phonological representations hypothesis. *J Exp Child Psychol* 1997;66:18–41
69. Morais J, Luytens M, Alegria J. Segmentation abilities of dyslexics and normal readers. *Percept Mot Skills* 1984;58:221–222
70. Bradley L, Bryant P. Visual memory and phonological skills in reading and spelling backwardness. *Psychol Res* 1981;43:193–199