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Evidence for aberrant auditory anatomy in developmental dyslexia

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ABSTRACT **Abnormal auditory processing in dyslexics suggests that accompanying anatomical abnormalities might be present in the auditory system. Therefore, we measured cross-sectional neuronal areas in the medial geniculate nuclei (MGNs) of five dyslexic and seven control brains. In contrast to controls, which showed no asymmetry, the left-side MGN neurons were significantly smaller than the right in the dyslexic sample. Also, as compared with controls, there were more small neurons and fewer large neurons in the left dyslexic MGN. These findings are consistent with reported behavioral findings of a left hemisphere-based phonological defect in dyslexic individuals.**

Developmental dyslexics have impaired reading skills despite normal intelligence, sensory acuity, motivation, and education. Though many consider dyslexia to be fundamentally a disorder of language, there is evidence that it is associated with perceptual abnormalities that could, by interfering with normal development, lead to the higher-order defects, including linguistic anomalies.

We previously reported that dyslexics have diminished visually evoked potentials to rapid, low-contrast stimuli, but normal responses to slow or high-contrast stimuli, consistent with involvement of the magnocellular but not the parvocellular division of the visual pathway (1). Furthermore, the neurons of the magnocellular layers of the lateral geniculate nucleus (LGN) were found to be on average 27% smaller in dyslexic brains (1). Following our report and also using evoked potential techniques Lemkuhle *et al.* (2) tested the spatial response characteristics of the magnocellular and parvocellular visual pathways and demonstrated dysfunction in the magnocellular but not the parvocellular stream. These findings provide a physiological basis for behavioral findings that developmental dyslexics do poorly in tests requiring rapid visual processing (3, 4). Because reports of abnormally slow auditory processing in dyslexics (5–19) suggest that a similar fast subsystem defect might be present in the auditory system as well, we measured cross-sectional neuronal areas in the medial geniculate nuclei (MGNs) of five dyslexic and seven control brains.

MATERIALS AND METHODS

The anatomical material in this study was identical to that employed in previous anatomical studies (1, 20), except for the addition of two control brains. We examined the MGN in autopsy specimens from five dyslexic subjects and seven nondyslexics. The dyslexic brains came from a heterogeneous group of subjects that were diagnosed in life with test batteries for intelligence and reading achievement. They lived during different time periods in different states of the United States and other countries and were diagnosed by different professional diagnosticians using slightly different testing instruments. In every case, however, there was a large discrepancy between intelligence (average or above in all cases) and reading achievement despite normal or enhanced educational opportunities. None had serious neurologic or psychiatric histories. Their medical histories and causes of death did not interfere with the examination of the brain. There were four right-handed males and one left-handed female [mean age, 34.8 ± 13.6 years (SEM)]. The control brains came from subjects with no history of reading disability and some had received sufficient testing during life to permit exclusion of the diagnosis of developmental dyslexia. The subjects had average or above average intelligence and normal or superior reading and academic achievement. None of the subjects had a diagnosed neurological disease. There were six right-handed males and one left-handed female (mean age, 49.9 ± 9.3 years). The age difference was not significant over the whole group; when female cases were excluded, the age difference was significant (control mean, 53.5 ± 10.1 years; dyslexic mean, 21.5 ± 3.8 years; $F_{1,8} = 6.12$, $P < 0.05$).

We used the Yakovlev method (21) for processing whole brains in serial histological sections identically in both groups. In brief, brains were embedded in celloidin and sectioned whole at 35 μm in the coronal plane, cutouts were taken that contained the MGN, and every 10th section was stained with cresyl violet for cell bodies and adjacent sections were stained with the Loyez method for myelin (21). Sections were coded and randomly right–left reversed so that the morphometrist was not aware of group (dyslexic versus nondyslexic) or side (right versus left). Similarly, in both groups and sets of hemispheres, extensive sampling of neurons, averaging 300 per brain, was carried out along the anteroposterior, mediolateral, and dorsoventral axes well within the borders of the MGN but without attention to architectonic subdivisions.

The bulk of the ovoid-shaped MGN is easily delineated in human brain sections stained either with cresyl violet or the Loyez method. Guided by studies in nonhuman primates (see ref. 22), we found in our human MGN sections two main nuclear subdivisions: a larger principal nucleus and a smaller magnocellular nucleus. The principal nucleus can be subdivided into posterodorsal, anterodorsal, and ventral divisions. Both the anterodorsal and ventral divisions contain large, medium, and small neurons. The magnocellular medial nucleus contains the largest cells, even larger than those of the adjacent suprageniculate nucleus, from which it can be separated. To a large extent these cytoarchitectonic regions were visible both in our normative and dyslexic material, but we chose not to study them separately because there were areas of subtle disorganization obscuring some borders in the dyslexic cases and we could not be sure we would be comparing equivalent areas. There is evidence of neuronal migration anomaly in the cerebral cortex of the dyslexic brains (see ref. 20), and we could not exclude this possibility in the MGN (23, 24). In addition, separate analyses of samples taken from the medial and lateral, dorsal and ventral,

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Abbreviations: LGN, lateral geniculate nucleus; MGN, medial geniculate nucleus; NS, not significant.

and anterior and posterior quadrants of the MGN did not find differences among these regions, so we collapsed the results over all quadrants.

Only neurons displaying a clearly visible nucleolus were measured. Cells were drawn by use of a camera lucida and measured with a Zeiss MOP-3 electronic planimeter coupled with a Macintosh Plus computer. Because of variability of cause of death, fixation, and processing time, there is substantial variation in tissue shrinkage in human autopsy material. Therefore, the methods do not lend themselves to accurate assessment of absolute neuronal size but are precise (intraobserver reliability = 0.98) and useful for right–left comparisons and comparisons between two groups of brains.

RESULTS

The results of the measurements are shown in Table 1 and Fig. 1. Using difference scores between the hemispheres (right minus left) as a dependent measure (25), we found an interaction between hemisphere and diagnosis. Specifically, there was significant right–left asymmetry in the dyslexic but not the nondyslexic group, with dyslexics having smaller left than right MGN neurons (Mann–Whitney U test; $Z = 2.0$; $P < 0.05$).

There was no overall difference in the mean neuronal area between dyslexics and controls. Therefore, cells were grouped according to area into bins increasing by 100 μm^2, thus producing about eight bins per MGN, and χ^2 values were calculated for the distribution of cells in these bins between dyslexics and controls overall and between right and left hemispheres within and between groups. The distribution of neuronal sizes differed between dyslexics and controls, with the dyslexic sample showing more small neurons and fewer large neurons ($\chi^2 = 65.3$, df = 7, $P < 0.001$). The distribution of neurons between left dyslexic and left control MGNs also differed, with dyslexics having more small and fewer large neurons ($\chi^2 = 91.17$, df = 7, $P < 0.001$; Fig. 1, *Upper Left*). The distribution of neurons between right dyslexic and right control MGN did not differ ($\chi^2 = 8.38$, df = 6, NS; Fig. 1, *Upper Right*). The distribution of right MGN neurons did not differ from that of left MGN neurons in the control sample ($\chi^2 = 9.14$, df = 7, NS; Fig. 1 *Lower Right*), but in the dyslexic sample the left MGN contained more small neurons and fewer large neurons than the right MGN ($\chi^2 = 55.33$, df = 6, $P < 0.001$; Fig. 1 *Lower Left*).

The two female cases (also the only left-handed cases) did not differ from their male cohorts, so they were included in the analysis. Similar results were obtained when the female cases were excluded from the analysis, except for the cell area by asymmetry by group interaction (Mann–Whitney U test; $Z = 1.8$, NS). The dyslexic sample still showed more small neurons and fewer large neurons overall ($\chi^2 = 45.2$, df = 7, $P < 0.001$). The distribution of neurons between left dyslexic and left control MGN also still differed, with dyslexics having more small and fewer large neurons ($\chi^2 = 73.44$, df = 7, $P < 0.001$; Fig. 1 *Upper Left*). The distribution of neurons between right dyslexic and right control MGN still did not differ ($\chi^2 = 12.56$, df = 6, NS). The distribution of right neuronal sizes did not differ from that of the left in the control sample ($\chi^2 = 8.89$, df = 7, NS); in the dyslexic sample there was a significant difference in the distribution of neuronal sizes between the left and right sides, with the former having fewer large neurons and more small neurons ($\chi^2 = 50.96$, df = 6, $P < 0.001$).

DISCUSSION

Measurement of kurtosis (size of the tails of a normal distribution) in our samples shows that the MGN neuronal areas in both dyslexic and control brains lie along curves with substantially smaller tails than the standard normal distribution (positive kurtosis). This could explain why a significant difference in the distribution of cell sizes could exist without its being reflected in different mean cell areas.

It is unlikely that the hemispheric differences in the dyslexic sample and the differences between the dyslexic and control samples reflect an artifact of tissue processing. The brains were processed whole with identical processing factors affecting both hemispheres. There were other regions in the same brains where no differences were found in the areas of neurons; for instance, the parvocellular LGN neurons did not differ between the dyslexics and controls, and neither the magnocellular nor the parvocellular LGN neurons differed between the hemispheres in either group (see ref. 1). Furthermore, measurements of cell sizes in area V1 disclosed lateral asymmetries in the control but not in the dyslexic cases, thus confirming present and previous findings of alterations in expression of cerebral asymmetry in dyslexic brains (20, 26).

It is also unlikely that the differences between dyslexic and control groups and between left and right hemispheres in the dyslexic group reflect some systematic bias in the plane of section—i.e., the cells are systematically measured in a more minor axis in dyslexics; if this were the case, we should also have seen a difference in the mean cell area, which we did not. Moreover, the results are not the same for both the hemispheres, which would imply that the cells in only one

Table 1. Mean cross-sectional areas of neurons of the MGN in the right and left hemispheres of dyslexic and nondyslexic brains

Group	Subject	Area, μm^2 [mean ± SEM (n)]	
		Right hemisphere	Left hemisphere
Dyslexic	ORT-1	206.69 ± 3.77 (295)	195.60 ± 3.53 (303)
	ORT-2	236.20 ± 4.23 (396)	204.95 ± 3.78 (420)
	ORT-5	253.34 ± 4.39 (381)	240.19 ± 4.70 (317)
	ORT-20	216.72 ± 3.83 (305)	203.56 ± 3.10 (458)
	ORT-30	258.17 ± 4.17 (335)	237.38 ± 4.12 (389)
Nondyslexic	ORT-7	229.11 ± 4.55 (167)	274.42 ± 4.91 (358)
	ORT-8	250.08 ± 3.53 (391)	224.36 ± 2.80 (441)
	ORT-9	250.19 ± 9.53 (83)	241.87 ± 13.00 (60)
	ORT-15	232.32 ± 3.65 (500)	262.63 ± 5.06 (288)
	ORT-18	199.53 ± 7.21 (66)	226.11 ± 7.29 (172)
	ORT-37	231.93 ± 3.99 (268)	236.15 ± 5.82 (197)
	STD-B1	234.69 ± 4.57 (295)	221.57 ± 3.56 (347)

Subjects are all right-handed males with the exception of ORT-20 and ORT-18, who are left-handed females.

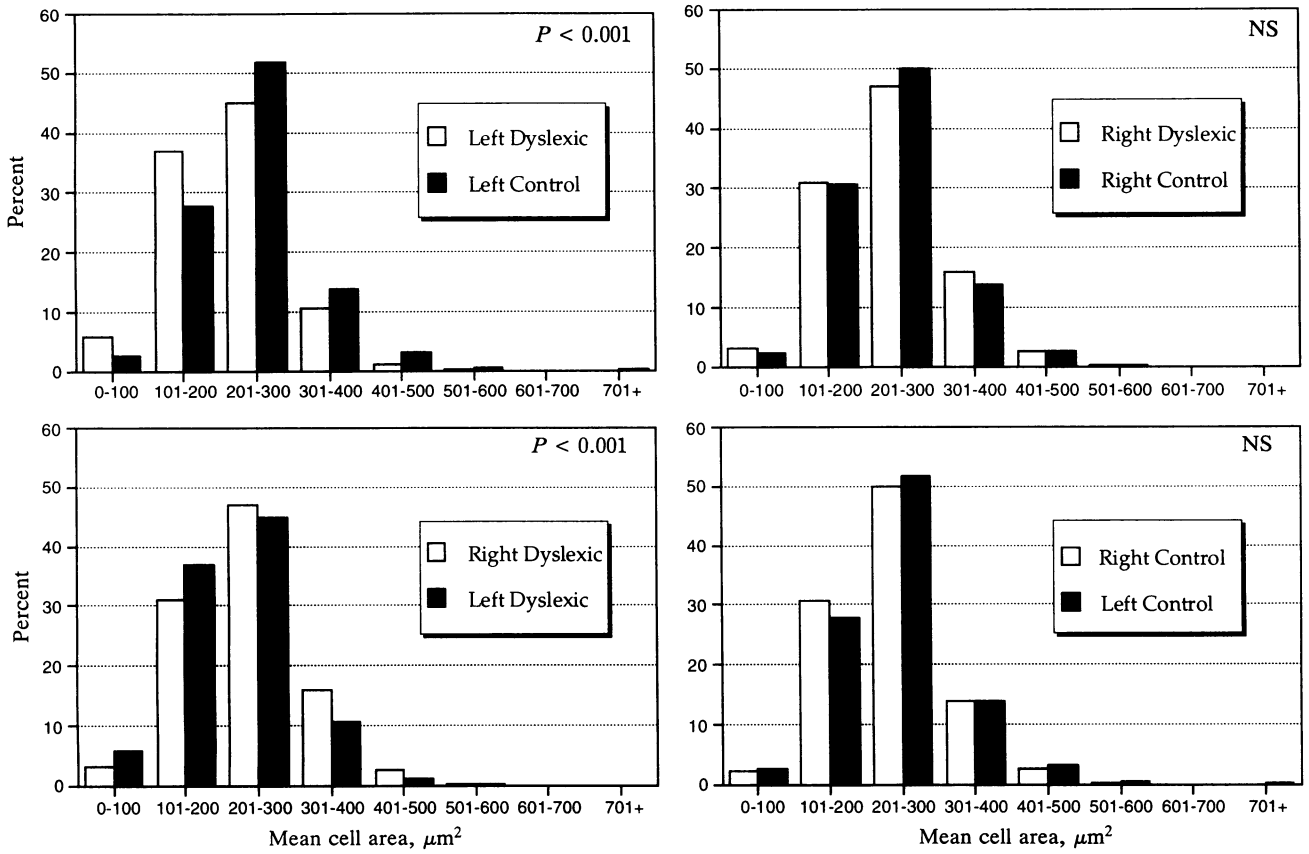

FIG. 1. (*Upper*) Percentage of total number of neurons belonging to progressive bins of 100 μm^2 in the nondyslexic and dyslexic right and left MGN. Whereas the left dyslexic MGN has more small neurons and fewer large neurons than the left control MGN ($\chi^2 = 91.17$, df = 7, $P < 0.001$), the right MGNs do not differ between the groups [$\chi^2 = 8.38$, df = 6, not significant (NS)]. (*Lower*) Percentage of total number of neurons belonging to progressive bins of 100 μm^2 in the nondyslexic and dyslexic right and left MGN. Whereas the dyslexics have more small neurons and fewer large neurons in the left MGN ($\chi^2 = 55.33$, df = 6, $P < 0.001$), the nondyslexics show no interhemispheric differences ($\chi^2 = 9.14$, df = 7, NS).

hemisphere were cut at an unfavorable angle, also an unlikely situation.

Several studies (5–19, 27–29) have suggested that the analysis of fast temporal auditory transitions, critical for language, is specifically handled by the left hemisphere: In dichotic listening studies, rapid acoustic stimuli show left hemisphere dominance; reduction of the rate of acoustic change diminishes lateralization. Tallal (30) 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 (31). Tallal (32) has suggested that the development of adequate reading competence depends on normal auditory perception. Webster *et al.* (33), Zinkus *et al.* (34), and others have reported pervasive language and reading disturbances in children with chronic, severe otitis media. Shucard *et al.* (13) found amplitude asymmetries of auditory evoked responses that were in opposite directions in dyslexics and controls, and Pinkerton *et al.* (10) 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 (35, 36). A high frequency of spelling errors was found to correlate with low auditory evoked potential amplitudes at P50 and P300 by Byring and Jarvilehto (6) and related findings have been reported by others [ref. 37; also see review by Obrzut *et al.* (8)].

We find that the brains of dyslexics show an abnormal MGN asymmetry. We cannot distinguish between changes in numbers of different types of neurons versus changes in size of particular neuronal populations to explain the changes we see in the distributions. We speculate that the phonological abnormalities described in dyslexic individuals may result from abnormal development of the auditory system in the left hemisphere—specifically, in the subsystem that handles rapid temporal transitions (27). The additional anatomic abnormalities found in language-related cortex (20) may be related to the abnormalities in the MGN reported here or may reflect some common underlying cause. We speculate that the present MGN findings are secondary to the cortical changes, reflecting abnormalities in cortical targets for axons arising in MGN during development. This hypothesis is being tested in an animal model (38).

In a previous study (1) we found in the dyslexics smaller neurons in the large-cell division of the LGN, so the present findings may represent a similar difference in a second sensory system. It would not be surprising to find that in dyslexics other sensory (and perhaps motor and cognitive) systems also showed differences in large-cell, possibly fast-processing, subsystems as well.

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