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may assume that letter-by-letter reading arises from a more general, nonorthographic perceptual deficit.^{7,8} This hypothesis, however, does not explain why graphically more complicated kanji characters were recognized almost perfectly by our patient. In addition, it is doubtful whether such a minimal deficit in visual perception, as in our patient, had a serious effect on kana reading. Probably, the left posterior occipital lobe including the lateral occipital gyri is functionally specialized to recognize kana characters in this patient.

Pure alexia selective for kana has not been reported. Although we believe that the responsible region lie in the lateral occipital gyri, the lesion seemed to affect the surrounding angular and inferior temporal gyri on SPECT. Conversely, pure alexia showing a greater impairment for nonwords was reported in Western countries in patients whose lesion involved the lateral occipital gyri.⁸⁻¹⁰ Further studies are required to determine the role of the lateral occipital gyri in reading.

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Preliminary evidence of widespread morphological variations of the brain in dyslexia

Article abstract—The MR images of 16 men with dyslexia and 14 control subjects were compared using a voxel-based analysis. Evidence of decreases in gray matter in dyslexic subjects, most notably in the left temporal lobe and bilaterally in the temporoparietooccipital juncture, but also in the frontal lobe, caudate, thalamus, and cerebellum, was found. Widely distributed morphologic differences affecting several brain regions may contribute to the deficits associated with dyslexia.

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Dyslexia affects 5 to 10% of school-aged children and can persist into adulthood. Structural brain-imaging studies in dyslexia have generally focused on the left temporal and parietal regions,^{1,2} whereas functional MRI and PET studies have revealed abnormal patterns of brain activity in the left temporal, parietal, and inferior frontal lobes.³⁻⁵ In this study, we sought to localize morphologic differences in dyslexia beyond the lobar level using a voxel-based analysis of whole-brain gray matter. Unlike the traditional volumetric analyses that compare the number of voxels in a

specific structure (thereby generating an absolute volume), voxel-based analyses compare the signal intensities of each voxel in a normalized brain to identify changes in tissue density. We used a voxel-based comparison because it offers the advantage of being able to determine a precise location of morphologic alterations without limiting the analyses within predefined neuroanatomic regions. Based on findings from a previous volumetric analysis of the same individuals with dyslexia used in the current study,² we predicted that gray matter reductions would be localized to the left inferior, middle, or mesial temporal subregions.

Methods. Sixteen right-handed dyslexic men, aged 18 to 40 years (mean 24 ± 5 years), were matched to a group of 14 control subjects for gender, age, educational level, handedness, socioeconomic background, and IQ. All subjects were screened for medical/neurologic disease and severe psychiatric disorders. Subjects being treated for attention deficit hyperactivity disorder were excluded.

All dyslexic subjects met *Diagnostic and Statistical Manual* (4th ed.) criteria for developmental reading disorder.

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Table Description of structures found in each significant cluster in statistical parametric mapping of control minus dyslexia contrast

Description of extent of cluster	Talairach coordinates of most significant voxel (x, y, z)	Cluster size, voxels	Z-score
Left superior temporal gyrus,* left angular gyrus, left occipital lobe	(-56, -54, 20)	1,685	5.54
Right* and left semilunar lobules of cerebellum	(18, -74, -38)	1,861	4.30
Left inferior frontal gyrus,* left orbital frontal gyrus	(-32, 28, -12)	1,255	4.03
Right precentral gyrus,* right inferior frontal gyrus	(66, -4, 24)	1,429	3.83
Left mesial temporal lobe,* left inferior temporal gyrus, left middle temporal gyrus, left superior temporal gyrus	(-30, -14, -24)	1,800	3.82
Medial right occipital lobe,* right angular gyrus, right superior temporal gyrus	(0, -96, -4)	5,039	3.73
Left* and right caudate, left and right thalamus	(-12, 26, -8)	1,438	3.57
Frontal pole,* left and right superior frontal gyrus	(0, 66, 8)	1,939	3.33

Voxel coordinates in Talairach space are listed with the associated Z-scores for the most statistically significant voxel within each cluster.

* Location of most significant voxel within each cluster.

der.⁶ All had at least average intelligence (Wechsler Adult Intelligence Scale-Revised Full Scale, Verbal and Performance IQ > 90) but showed persistent reading deficits, despite prior treatment with interventions ranging from tutoring to special education. All scored 8 or lower on the passage (decoding) score of the Gray Oral Reading Test (3rd ed.; GORT-3) using norms for the ceiling of the test: a 12.9 grade level and age of 18.9 years. The cutoff applied is 0.67 of a SD below average for high school seniors.

Control subjects were free of any history of developmental disorder, attention deficit disorder, special education, and reading or spelling deficits confirmed by scores from the GORT-3 and Wide Range Achievement Test (3rd ed.) Reading and Spelling subtests. Informed consent was obtained from all subjects.

The dyslexic and control groups in this study participated in a previous volumetric study.² Fourteen of the 16 dyslexic men and 12 of the 14 control subjects studied here also participated in functional brain-imaging studies, which provided evidence of functional variations in the left and right temporal lobe and inferior parietal cortex in the men with dyslexia.^{4,5}

Brain MR images were acquired with a GE Signa 1.5 T scanner (Milwaukee, WI). Coronal spoiled gradient echo images with the following parameters were acquired: repetition time = 24 ms, echo time = 5 ms, flip angle = 45°, number of excitations = 1, matrix size = 256 × 192, field of view = 24 cm, and slice thickness = 2 mm for 124 slices. Statistical analyses were conducted with SPM99 (Friston & Ashburner, Institute of Neurology, London, UK) with previously described methods.⁷ Each subject's brain volume was imported into SPM99 and warped into Talairach space using an automated linear transformation. Each

brain was then segmented into gray matter, white matter, and CSF using standard SPM algorithms. The gray matter volumes were then smoothed with an 8-mm full width at half-maximum isotropic Gaussian kernel to decrease spatial noise and anatomic variability. Images were scaled to a global mean intensity of 100 for each subject. Voxel-by-voxel unpaired *t*-tests ($p < 0.05$) were used to compare signal intensities between groups. To determine the presence of significant clusters, an extent threshold ($p < 0.05$) was used to correct for spatial correlations in the data.

Results. The table presents the Talairach coordinates of the most significant voxel within each cluster where control subjects showed greater signal intensity for gray matter than subjects with dyslexia. Conversely, the dyslexic group showed no significant clusters of greater signal intensity compared with the control group.

A large significant cluster was located in the left posterior superior temporal gyrus (STG) and temporoparietooccipital region (figure). A second large cluster of significant voxels covered the left inferior, middle, superior, and mesial temporal regions. Significant decreases in gray matter also were seen in the right parietooccipital juncture and right STG. In the frontal lobes, subjects with dyslexia showed significant reductions in gray matter in the left orbital gyrus and frontal pole and bilaterally in the inferior frontal gyrus and superior frontal gyrus. The cluster in the right inferior frontal gyrus also extended into the precentral gyrus. Within the subcortical nuclei, subjects with dyslexia showed a bilateral decrease of gray matter in the head of the caudate and thalamus. A reduction in gray matter also was found in the semilunar lobules of the cerebellum of the subjects with dyslexia.

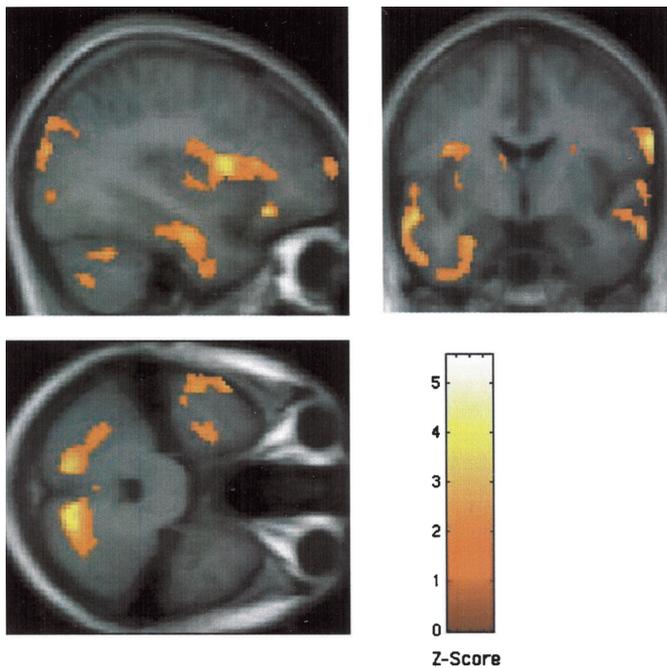


Figure. Significant voxels (height threshold, $p < 0.05$; extent threshold, $p < 0.05$) representing differences in gray matter density between subjects with dyslexia and control subjects as they occur on representative slices of an average control brain.

Discussion. In a previous volumetric study using the same sample, we noted a decrease in the left temporal lobe tissue in men with dyslexia compared with control subjects but failed to find any significant differences in left STG.² Based on these findings, we predicted that a voxel-based analysis would further localize left temporal lobe gray matter reductions associated with dyslexia to inferior, middle, or mesial subregions. However, the voxel-based results in this study indicated that the variation in neuroanatomy is, in fact, widely distributed throughout the left temporal lobe in dyslexia with gray matter differences observed in the superior, middle, inferior, and mesial temporal structures.

At a cursory level, our finding of decreased gray matter density of the STG in dyslexia appears to contradict our earlier report² that observed no volumetric abnormalities in this region. However, compared with volumetric analyses, the voxel-based technique used in the present study incorporates a methodological approach that is more likely to be sensitive to both subtle and widespread group differences in neuroanatomy. Further contributing to the difference in findings is the operational definition of the STG used earlier.² This definition did not include the posterior portions of this region, where most of the voxel-based morphologic differences were observed in the present study. Differences in the algorithms used to segment the brain into component tissue types also may have contributed to differences in results. Overall, the findings in this report are

consistent with previous functional imaging studies on dyslexia that have described abnormal patterns of activation elicited by phonological tasks in the middle and inferior regions of the left temporal lobe as well as the STG.^{4,8}

An unexpected finding of this study was the reduction of gray matter in the cerebellum and in the caudate. Recent studies have implicated the cerebellum in perceptual and cognitive processes including semantic and phonological processing.⁹ Although the caudate has traditionally been associated with motor control, its interconnections to the prefrontal cortex suggest that it might also be involved in higher-order cognitive processing and procedural learning.¹⁰ Further functional imaging studies are needed to determine how the caudate might directly or indirectly contribute to deficits associated with dyslexia.

Reading is a complex activity that involves multimodal component operations and requires the use of widely distributed areas of the brain. Several different sensory areas have been implicated in dyslexia.^{5,11} Whereas our results implicate several neurofunctional systems and widely distributed morphologic differences in dyslexia, they also may reflect anatomic variability within the dyslexic population. If a heterogeneous neurobiological substrate is indicative of diverse deficits in dyslexia, further studies in which subpopulations are identified through finer neurofunctional testing might determine the nature of neuroanatomic variability in developmental reading disorders.

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