Original Article

Lobar Asymmetries in Subtypes of Dyslexic and Control Subjects

Janet N. Zadina, PhD; David. M. Corey, PhD; Renee M. Casbergue, PhD; Lisa C. Lemen, PhD; Jeffrey C. Rouse, MD; Tracey A. Knaus, PhD; Anne L. Foundas, MD

ABSTRACT

Reading involves phonologic decoding, in which readers "sound out" a word; orthographic decoding, in which readers recognize a word visually, as in "sight reading"; and comprehension. Because reading can involve multiple processes, dyslexia might be a heterogeneous disorder. This study investigated behavior and gross lobar anatomy in subtypes of dyslexic and control subjects. Subjects aged 18 to 25 years with identified reading problems and a group of healthy controls were given cognitive and behavioral tests and volumetric brain magnetic resonance imaging (MRI). Because atypical cerebral laterality has been proposed as a potential neural risk for dyslexia, dyslexic and control subjects were compared on anatomy of gross lobar regions. On asymmetry quotients, no significant differences were found between groups. Examination of the percentage of total brain volume of each structure revealed that control and dyslexic subjects were significantly different ($P = .018$). Dyslexic subjects had a larger percentage of brain volume than did the controls in the areas of total prefrontal ($P = .003$; 9.30% larger) and superior prefrontal ($P = .004$; 11.48% larger region). A Pearson correlation was performed to investigate whether a relationship existed between behavioral measures and either volumes of total prefrontal and total occipital regions or asymmetry quotients. A significant positive relationship between the left total occipital and word identification performance existed ($R = .452$, $P = .045$). Because it is believed by some that dyslexia occurs in varying degrees of severity, and because one of the research questions in this study is whether anatomy relates to severity or to distinct biologic groups, subjects were grouped according to both the nature and distinct pattern of reading or language performance and the degree of deficit. A battery of reading tests revealed five clinical subgroups of control (two) and dyslexic (three) subjects. These subgroups were statistically different on all cognitive and behavioral measures. When asymmetry was investigated across subgroups, significant differences between

Received April 26, 2005. Received revised August 3, 2005. Accepted for publication Sept 25, 2005.

From the Department of Psychiatry and Neurology (Drs Zadina, Corey, Rouse, Knaus, and Foundas), Tulane University Health Sciences Center; New Orleans, LA; Department of Psychiatry and Neurology, University of New Orleans (Dr Casbergue), New Orleans, LA; Department of Curriculum and Instruction, Louisiana State University Health Sciences Center (Dr Lemen), New Orleans, LA; and Department of Radiology, Veterans Affairs Medical Center (Drs Lemen and Foundas), New Orleans, LA.

This work was supported in part by the NIH Charity Tulane-Louisiana State University General Clinical Research Center.

This research was conducted at the University of New Orleans, Tulane University Health Sciences Center, and University Hospital of Louisiana State University. It was presented at the American Educational Research Association annual meeting in San Diego, CA, 2004.

Address corresponence to Dr Janet N. Zadina, Department of Psychiatry and Neurology, Tulane University Health Sciences Center, 1440 Canal Street, Tidewater TB52, New Orleans, LA 70112. Tel: 504-988-2241; fax: 504-988-3695; e-mail: jzadina1@tulane.edu.

subgroups were found at the multivariate level ($P = .043$). Only the phonologic deficit groups (weak phonologic controls, phonologic deficit dyslexic subjects) had atypical asymmetry patterns. This finding suggests that lack of subtyping could have confounded earlier studies and that anomalous asymmetry might be related to phonologic dyslexia, whereas other subtypes might be reflective of environmental factors. Examination of volume at the subgroup level also showed differences between subgroups that might have implications for the nature of compensation. This study supports the concept that anomalous anatomy might reflect anomalous functional cerebral laterality, which could be a risk factor for developmental dyslexia, varying according to the nature of the deficit. (*J Child Neurol* 2006;21:922–931; DOI 10.2310/7010.2006.00195).

The human brain is anatomically and functionally asymmetric. Discrete brain regions, such as the planum temporale and portions of the inferior frontal gyrus that mediate speech and language functions, have been found to be larger in the left cerebral hemisphere in the majority of healthy adults.[1,2] Although there are limited data about a direct relationship between these anatomic and functional interhemispheric differences,[3,4] there has been speculation that these leftward asymmetries reflect the left hemispheric dominance for speech and language functions. Gross lobar asymmetries have also been found, with about 70% of healthy adults having larger right than left prefrontal and larger left than right occipital lobe protuberance. Evidence to support these gross lobar asymmetries comes from postmortem[5] and neuroimaging studies, including computed tomography (CT)[6–8] and magnetic resonance imaging (MRI) scans.[9,10] Reduced or reversed lobar asymmetries have been found in individuals with neurodevelopmental disorders, including dyslexia, specific language impairment, and developmental stuttering.[11–17] Therefore, these population-level asymmetry patterns of a rightward prefrontal and leftward occipital asymmetry have been considered typical, and variation from these more typical anatomic configurations has been considered anomalous or atypical.

As early as 1927, Orton hypothesized that atypical cerebral laterality (eg, right hemispheric or bilateral language dominance) might be a risk factor for developmental language disorders, such as dyslexia.[18] Geschwind and Galaburda developed an overarching hypothesis-driven theory of cerebral laterality that offers a potential anatomic explanation for Orton's original hypothesis.[19] The Geschwind-Galaburda conceptual model states that hemispheric dominance is a result of influences on fetal brain development, particularly that of testosterone or immune-related factors. They postulated an association between learning disorders, anomalous brain asymmetry, immune disorders, and non-right-handedness and hypothesized that androgenic hormones might disrupt the formation of typical cerebral asymmetries and thus be a factor in developmental language disorders. Underlying this hypothesis is the theory that anatomic asymmetry (leftward asymmetry of language-related cortex) and functional lateralization (left-hemisphere dominance for language) are related. Therefore, reduced or reversed prefrontal and occipital lobar asymmetries might be associated with atypical cerebral laterality, which, in turn, might increase susceptibility to developmental language disorders such as dyslexia.[20]

A few studies have examined these lobar asymmetries in individuals with dyslexia. In a CT scan study of 24 subjects with dyslexia, Hier and colleagues found a subgroup of 10 individuals with reversed or atypical rightward occipital lobe asymmetry.[11] These 10 subjects had lower mean Wechsler Verbal IQ scores than the 14 subjects with typical leftward occipital asymmetry. Although speculative, Hier et al suggested that this atypical occipital asymmetry might be a marker of atypical cerebral laterality. In another CT scan study, frontal and occipital lobe asymmetries were studied in 26 dyslexic boys.[12] The dyslexic cohort had more symmetric or atypical occipital widths compared with the healthy controls. Neither Wechsler Verbal IQ nor Wechsler Performance IQ was related to cerebral size or asymmetry patterns.

Using MRI methodologies, Hynd et al examined anterior and posterior asymmetries in 10 dyslexic children, 10 children wtih attention-deficit disorder/attention-deficit hyperactivity disorder (ADD/ADHD), and 10 matched control children.[15] They found that both dyslexic children and children with ADD/ADHD had significantly smaller right-hemisphere anterior (frontal) widths compared with healthy, matched controls. Thus, these diagnostic groups had a lack of asymmetry or more anomalous lobar anatomy. In another MRI study of 21 dyslexic adults and 29 controls, a reversal of typical asymmetry (rightward) was found in the posterior (occipital) region in the dyslexic subjects and no group difference was found in the anterior (frontal) region.[16]

Prefrontal and occipital lobar asymmetries have also been studied in developmental stuttering. Because stuttering is a developmental speech-language disorder, the findings from these studies might have some implications for dyslexia research and might offer further support for the notion that atypical lobar asymmetry patterns can be associated with atypical function. Strub et al studied CT scan lobar asymmetry in two siblings with developmental stuttering and found atypical (symmetry) anatomy of the occipital lobes.[14] In a volumetric MRI study of 16 adults with persistent developmental stuttering and 16 controls, Foundas et al found atypical asymmetries in the stutter group but not in the fluent matched control group.[25] Reduced size was associated with subtle linguistic deficits in the stutter group. Based on these results, Foundas postulated that atypical cerebral laterality, reflected by this atypical prefrontal and occipital lobar anatomy, could be an etiologic factor in developmental stuttering.

As earlier reviews of structural studies of dyslexia indicate, dyslexia research is plagued by inconsistent findings with regard to anomalous asymmetry and by the confound of heterogeneous dyslexic subjects.[21,22] It is possible that the cohorts of dyslexic subjects in previous studies were composed of subtypes of dyslexic subjects, such as phonologic, orthographic, or semantic.

It could be that one subtype exhibits extreme or reversed asymmetry and another subtype exhibits more symmetric structures, depending on the underlying impairment. Certain brain regions might be anatomically atypical, whereas other brain regions might not differ from controls. Thus, various combinations of anatomic configurations can be found in different diagnostic subgroups. Alternative hypotheses include the finding that a specific region of interest would be atypical in all individuals with dyslexia (indicating specificity of anatomic risk), or a number of regions can be anomalous, indicating that dyslexia might be a result of multiple combinations of anatomic anomalies (frequency effect). It could be that anomalous anatomy in one specific brain region or in multiple regions might be associated with a more severe form of dyslexia.

The major goal of this study was to determine whether classifying young adults with a diagnosis of dyslexia and healthy, matched controls into subtypes based on separable reading deficits would reveal differences on anatomic measures (prefrontal and occipital lobe size and asymmetry) that did not show up in the broad groups of dyslexic and control subjects and to learn whether these anatomic measurements correlate with performance on cognitive and behavioral tests of reading ability. To our knowledge, only one other published anatomic study[23] and one published functional study[24] classified the dyslexic cohort into diagnostic subgroups. We do not know of any other study that has separated the control subjects into a subgroup of strict controls and a subgroup that might be compensated dyslexic subjects (ie, weak phonologic controls). Thus, the results from earlier studies could have been confounded by the inclusion of compensated dyslexic subjects in the control cohort, as well as the inclusion of mixed reading deficits in the dyslexic subgroup. Furthermore, some studies could have included poor readers who might be poor readers not because they are dyslexic but owing to more global factors.

The major hypothesis was that adults with dyslexia would have anomalous prefrontal and occipital lobe anatomy compared with controls and that this anomalous anatomy might differ according to reading deficits (subgroups). Since approximately 70% of adults have lobar asymmetry consisting of a larger right prefrontal and larger left temporoparieto-occipital region, symmetry or reversal of those typical asymmetry patterns would be considered anomalous anatomy, and this anomalous anatomy might be a neural risk for atypical function.[17,25] However, since heterogeneous cohorts in earlier studies could have washed out anatomic differences that might be related to separable reading deficits, in this study, the anatomy was investigated in two stages. First, the broad groups of dyslexic and control subjects were analyzed for anomalous prefrontal and occipital anatomy. After reading tests determined behavioral subtypes with separable reading deficits, additional language and cognitive tests were administered to support the behavioral subtypes identified by the reading tests. Anatomy was investigated within and across the subtypes to see if the subtyping would reveal differences not seen in the broad group analysis. Therefore, three questions were asked: (1) Will analysis of anatomy by subgroups reveal differences in the asymmetry distributions not seen in the analysis of the broader classification of dyslexic and control subjects? (2) Will the volume of prefrontal and occipital regions differ between control and dyslexic subjects and between individual subgroups? (3) Will any differences in these measures between dyslexic and control subjects or individual subgroups correlate with their performance on cognitive and behavioral measures? Because anomalous prefrontal asymmetry was seen in dyslexic subjects in an earlier study,[15] it was predicted that dyslexic subjects would have anomalous prefrontal asymmetry. Because an earlier study showed that anomalous occipital asymmetry might be related to anomalous planum temporale asymmetry,[13] which, in turn, has been found in some studies of individuals with dyslexia,[1,26] it was hypothesized that the dyslexic subjects would have anomalous occipital lobe asymmetry. It was predicted that the two phonologic subtypes would exhibit similar anatomic anomalies that would differ from the other subtypes. It was also predicted that anomalous anatomy would be associated with impaired performance on the tests of reading ability.

METHODS

Subjects

Thirty-two college students ages 18 to 25 years were examined, including 16 adults with dyslexia and 16 controls. All participants were native English speakers, and groups were matched for age (dyslexic subjects: 20.69 years, SD 1.44 years; controls: 20.00 years, SD 1.86 years), education (dyslexic subjects: 13.33 years, SD 0.60; controls: 13.87 years, SD 1.09 years), and sex (dyslexic subjects: 11 female, 5 male; controls: 9 female, 7 male). All participants were right-handed, and groups were matched on the degree of handedness based on the Briggs and Nebes Handedness Inventory.[27] Individuals with neurologic disease, a psychiatric history, other developmental disorders, or a history of significant head injury were excluded from participation in this study. Because the MRI scanner generates a strong magnetic field, individuals with metal in their bodies (such as surgical clips or plates, bone pins, or metal iron filings) were not allowed to participate. No pregnant women or adults with known claustrophobia were allowed to participate. All potential participants were given a telephone interview to screen for inclusion and exclusion criteria. At the time of the first visit, questions were answered, and informed consent was obtained.

An interview and a battery of reading and cognitive and behavioral tests were administered to all participants. The test battery consisted of measures of general intelligence (Wechsler Verbal, Performance, and Full-Scale IQs), reading (phonologic, orthographic, and semantic measures), and language (listening comprehension and vocabulary).

Subjects were recruited who were currently in developmental reading classes in college, as well as those who placed out of developmental reading classes to ensure a range of reading ability. Reading was evaluated using the Woodcock-Johnson Psychoeducational Battery-III[28]: The Achievement Battery, Reading-Writing Subtest; Test 1: Letter-Word Identification (orthography); Test 9: Passage Comprehension (semantics, comprehension); and Test 13: Word Attack (phonology). The Woodcock-Johnson Psychoeducational Battery-III subtests have been shown to be effective in distinguishing the language weaknesses of learning-disabled college-aged subjects.[29]

Operational Definition of Dyslexia

Historically, dyslexia has been defined using a discrepancy (between IQ and reading ability) and a deficiency (poor reading performance) definition. Both of these definitions have merit. In the present study, we decided to use a deficiency definition based on a discrepancy between

performance across multiple reading measures rather than the discrepancy definition based on the discrepancy between IQ and reading ability. Given that one of the aims of this study was to investigate subtypes of dyslexia, it could be that IQ would vary according to subtype. It could be that low scores on the IQ test are a consequence of reading disability[30] rather than causative of reading disability. Because reading and IQ might have a mutually reinforcing relationship (Matthew effect), it would be invalid to base the definition of dyslexia on a related variable.[31] If this effect exists, IQ scores would be expected to decline as dyslexic children get older. Because this study used dyslexic subjects aged 18 to 25 years who might have been less likely to read over the years and to acquire new vocabulary, this effect could exist within this sample, rendering a discrepancy definition less effective than a deficiency definition. Discrepancies between reading measures defined the subtype, and our inclusion criteria might be a more accurate way to define dyslexia in college students.

Dyslexia was defined broadly as performance below a standard score of 90 (mean 100, SD 15) on one of three reading measures (phonologic decoding, orthography, and passage comprehension), similar to an earlier study of subtypes of college-aged dyslexic subjects.[23] When college students perform at or below a standard score of 90, they are performing several years below grade level on these reading subtests. Whereas most of the subjects were 1 SD or below on the reading measures, a few subjects had a substantial difference between one reading measure and the others, even though they were between 85 and 90 on the lowest measure.

Classification of Subtypes

Subtypes within the dyslexic and control groups were identified so that these subgroups could be examined independently with the goal of establishing a validated classification system that could be used in future research studies. The reading tests were chosen to reveal reading impairment in three processes based on a three-route model of reading: phonologic, orthographic, and semantic.[32] The reading battery revealed five clinical subgroups (two control and three dyslexic subgroups) (Table 1). There is a consensus that a phonologic subtype exists. Therefore, phonologic deficit dyslexia was defined as one subtype based on a deficiency in phonology (word attack standard score < 90) with passage comprehension and orthography considered intact based on scores ≥ 90. The nonphonologic deficit dyslexic ($n = 3$) subtype had impaired word identification or passage comprehension (< 90 standard score) with intact word attack (≥ 90 standard score). Finally, a global deficit dyslexic group ($n = 3$) was identified as subjects impaired on all three reading measures (< 90 standard score). This subtype could have multiple deficits or a broader diagnosis that might be a result of environmental, instructional, or cognitive deficits. Their "removal" as a result of being categorized as a subtype improves the homogeneity of the other subtypes. Within the controls, two subtypes were identified: strict controls ($n = 12$) with no reading deficit (all scores > 90 standard score) and weak phonologic controls ($n = 4$), good readers who had a phonologic score (word attack) of under 95 standard score (below age level) but not below 90 ($90 < 95$) standard score, who might represent compensated dyslexics. These subgroups were statistically different on all cognitive and behavioral measures.

MRI Procedures

Anatomic measurements were performed in vivo using advanced MRI methods. All subjects had volumetric MRI head scans performed at the MRI unit at University Hospital, New Orleans, Louisiana. MRIs were acquired on a General Electric (Milwaukee WI) 1.5-Tesla Signa Scanner with a T_1-weighted rapid gradiont echo imaging sequence as a gapless series of 124 contiguous sagittal images (1.5 mm slice thickness) with a field of view of 240 mm, 20-degree flip angle, and a 256×256 pixel matrix. This technique provides a three-dimensional view that allows measurement of the full volumetric extent of the functionally specific anatomic regions of interest.

Seven regions of interest were measured in all participants, including total brain volume and total prefrontal, superior prefrontal, inferior prefrontal, total occipital, superior occipital, and inferior occipital regions (Figure 1). This method is similar to that used to measure postmortem brains[5] and in a recent MRI study.[25] Measurements of each region of interest were done in the sagittal plane using the *Scion* image program (personal computer version of *NIH Image*[33]) in real space, with no warping of the images. A subset of five brains was measured by two researchers to establish interrater reliability through intraclass correlation (*SPSS*, version 10.0, SPSS Inc, Chicago, IL). A reliability coefficient of .85 was considered acceptable. Interrater reliability was established for all seven regions of interest measured, and the intraclass correlation coefficient for any given region was at least .88.

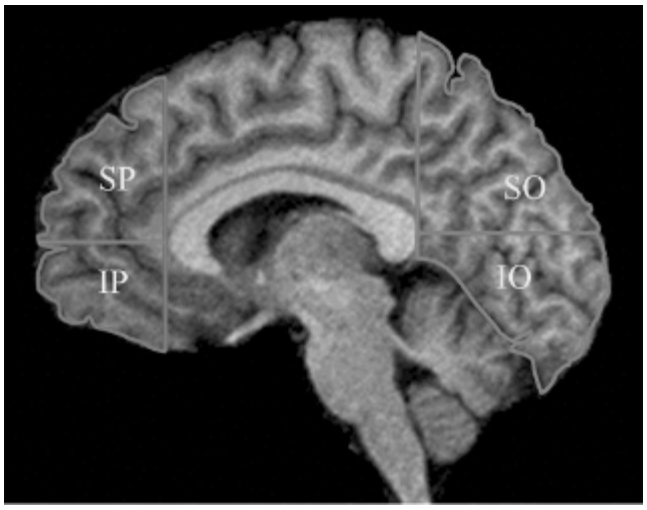

Figure 1. Regions of interest. IO = inferior occipital; IP = inferior prefrontal; SO = superior occipital; SP = superior prefrontal.

Table 1. Means (SD) of Subgroups on Specific Measures of Reading

	Controls		*Dyslexics*		
Reading Measure	*C*	*WPC*	*PDD*	*NDD*	*GDD*
Phonology	105.83 (08.71)	92.25 (01.50)	77.20 (07.98)	93.67 (06.35)	66.33 (12.01)
Orthography	104.25 (08.07)	97.00 (04.83)	85.60 (08.24)	88.67 (00.58)	78.33 (05.51)
Semantics	118.58 (11.52)	106.75 (04.99)	94.10 (02.77)	98.00 (09.00)	75.00 (11.53)

C = strict controls; GDD = global deficit dyslexics; NDD = nonphonologic deficit dyslexics; PDD = phonologic deficit dyslexics; WPC = weak phonologic controls.

Total Brain Volume

Measurement of the hemisphere was accomplished using a mouse-driven cursor to trace the outer boundary of the cerebral hemisphere, beginning with the midsagittal slice and continuing on every fourth slice to the most lateral extent of the hemisphere. The tracing conformed to the topography of the gyri. The depth of each gyrus was traced unless an adjacent gyrus was closely opposed. This method has been found to be reliable in other studies[6,9,34] and is similar to the method reported in Foundas et al.[25] Both hemispheres were measured in each subject, with half of the midline slice allocated to each hemisphere. To compute the total brain volume, the surface area was multiplied by the image thickness.

Prefrontal Lobe Volumes

Left- and right-hemisphere images were measured in each subject. The prefrontal cortex is primarily the heteromodal association cortex and is anatomically defined as the area of the frontal lobe rostral to the precentral gyrus, including portions of the superior, middle, and inferior frontal gyri. It does not include primary and premotor cortical areas. The rostral boundary is defined as the most rostral extent of the frontal cortex visible on each sagittal image extending to the frontal pole. Prefrontal lobe volumes were measured on the same slices as the total brain volume measurements. A vertical line was drawn on the most rostral extent of the genu of the corpus callosum visible on the midsagittal slice, and the coordinates corresponding to that location defined the caudal boundary on every sagittal image were measured to the lateral extent of each hemisphere

Superior and Inferior Prefrontal Volumes

Using the same methods on the same images, a horizontal boundary between the superior and inferior portions was established using the most rostral point of the corpus callosum (see Figure 1). Contained within the superior prefrontal region are portions of the superior and middle frontal gyri, including the dorsolateral prefrontal cortex and the rostral extent of the supplementary motor cortex and parts of the anterior cingulate. The inferior prefrontal region included parts of the inferior and orbitofrontal cortex.

Occipital Volumes

Starting on the midsagittal image and measuring on every fourth image, the same tracing method was used to obtain occipital volumes. A vertical line was drawn from the most caudal point of the corpus callosum on the midsagittal image, and the resulting coordinates were used as a boundary from the midsagittal image to the occipital pole. This boundary results in a larger occipital lobe than defined in earlier studies, and the regions of interest were composed of portions of the occipital and parietal cortex.

Superior and Inferior Occipital Volumes

To divide the superior occipital region from the inferior occipital region, a horizontal line was drawn from the most caudal point of the corpus callosum to the end of the occipital pole and the resultant coordinates were used to measure on every fourth image to the lateral extent of each hemisphere. This division resulted in the superior occipital subregion containing portions of the occipital lobe and the inferior parietal lobule and the inferior occipital subregion containing portions of the occipital lobe and the posterior-ventral temporal lobe.

Data Coding

Three measures were analyzed: proportional volumes, interhemispheric asymmetry quotients, and anatomic and behavioral relationships. Volumes were computed by multiplying the surface area by the image thickness, with half of the midsagittal image measure included in the right-hemisphere volume and half in the left-hemisphere volume. The proportion of volume to the total brain volume was computed, and the prefrontal and occipital volumes were obtained by converting prefrontal and occipital volumes to percent total hemispheric volume measures for each hemisphere using the following formula:

$$\text{Left\%} = 100^{*}\frac{\text{Left volume}}{\text{Left total hemispheric volume}}$$

Using these volumes, asymmetry quotients (AQ) were obtained for total hemisphere volume, prefrontal region (total, superior, inferior), and occipital region (total, superior, inferior) using the following formula:

$$\text{AQ} = \frac{\text{Left volume} - \text{right volume}}{(\text{Left volume} + \text{right volume})^{*}0.5}$$

Asymmetry quotients were used to classify each subject for the direction of asymmetry as follows: (1) rightward asymmetry (right > left): asymmetry quotient < −0.025; (2) symmetry (right = left): −0.025 < asymmetry quotient < 0.025; or (3) leftward asymmetry (left > right): asymmetry quotient > 0.025, similar to other studies conducted by our laboratory and others.[34–36]

RESULTS

All statistical analyses were performed using *SPSS*, and significance was considered as $P < .05$. Group membership and subgroup membership were considered independent variables. Chi-square analysis showed no significant differences on age, education, and sex measures between control and dyslexic subjects.

Anatomic Results for Broad Groups of Dyslexic and Control Subjects

To determine whether there were group differences on anatomic asymmetries, a one-way multivariate analysis of variance (ANOVA) was performed to compare the dyslexic ($n = 16$) and the control ($n = 16$) subjects on asymmetry quotients. There were no significant differences at the multivariate or univariate level.

To learn whether prefrontal and occipital lobe volumes differed between groups, a two-way repeated-measures multivariate ANOVA was used to evaluate the effect of group (control and dyslexic subjects) on volume (total prefrontal, superior prefrontal, inferior prefrontal, total occipital, superior occipital, inferior occipital), with hemisphere (left, right) as the repeated measure and group as the independent variable. No significant differences in overall hemisphere volumes were found, that is, the total left and right hemisphere and total brain volumes did not differ between the groups (see Table 2 for means and standard deviations).

Lobar volumes, however, were significantly different at the multivariate level ($P = .018$). To investigate which specific regions were contributing to this significant difference, an ANOVA was performed for each region of interest with hemisphere as the repeated measure and group as the independent variable. These analyses indicated that the dyslexic subjects had a larger percentage of total prefrontal ($P = .003$) and superior prefrontal ($P = .004$) volume compared with the

Table 2. Mean Volumes (SD) by Group

	Region of Interest (hemisphere)												*Asymmetry Quotients*	
	TPF		*SPF*		*IPF*		*TO*		*SO*		*IO*			
Group	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Frontal AQ*	*Occipital AQ*
Strict controls (n = 12)	12.52 (1.18)	13.00 (1.51)	7.19 (.82)	7.57 (1.13)	5.33 (0.56)	5.43 (0.54)	30.72 (2.88)	29.86 (3.15)	15.20 (2.07)	15.29 (2.00)	15.53 (1.76)	14.57 (2.02)	−0.04 (0.16)	0.02 (0.07)
Weak phonologic controls (n = 4)	13.23 (0.52)	12.97 (0.907)	7.37 (0.45)	7.41 (0.26)	5.86 (0.72)	5.56 (0.78)	32.35 (3.66)	31.76 (3.87)	16.90 (2.92)	16.74 (2.89)	15.44 (0.95)	15.01 (1.64)	0.03 (0.06)	0.03 (0.03)
Phonologic deficit dyslexics (n = 10)	14.23 (1.76)	14.14 (1.15)	8.36 (1.12)	8.28 (0.83)	5.87 (0.80)	5.87 (0.59)	29.96 (1.43)	30.07 (2.81)	15.37 (2.07)	15.79 (2.49)	14.59 (1.58)	14.28 (1.68)	0.01 (0.15)	0.01 (0.10)
Nonphonologic deficit dyslexics (n = 3)	13.93 (0.56)	14.79 (1.43)	8.23 (0.93)	8.44 (1.53)	5.70 (0.64)	6.36 (0.32)	30.00 (2.80)	29.64 (2.48)	16.56 (1.06)	15.93 (1.83)	13.44 (2.82)	13.71 (1.07)	−0.04 (0.08)	0.32 (0.11)
Global deficit dyslexics (n = 3)	13.04 (0.68)	13.41 (1.30)	7.49 (0.51)	8.16 (0.57)	5.55 (0.88)	5.25 (1.23)	28.65 (2.49)	27.48 (3.56)	13.95 (2.21)	14.19 (2.28)	14.70 (0.36)	13.29 (1.28)	{1299} 0.04 (0.07)	0.03 (0.10)

AQ = asymmetry quotient; IO = inferior occipital; IPF = inferior prefrontal; SO = superior occipital; SPF = superior prefrontal; TO = total occipital; TPF = total prefrontal.

control subjects. On average, prefrontal volumes were 9.3% larger in the dyslexic subjects compared with the control subject, and the superior prefrontal volumes were 11.48% larger.

Subtyping Analysis and Behavioral Test Results

Descriptive statistical analysis of means and standard deviations was computed for groups and subgroups on all behavioral measures (Table 3). Using multivariate ANOVA, the two broad groups of dyslexic and control subjects were examined on cognitive measures. The groups differed significantly on all variables, with the dyslexic group having lower scores on the Wechsler Verbal IQ ($F(1,30) = 10.552$, $P < .003$), Wechsler Performance IQ ($F(1,30) = 8.523$, $P < .007$), Wechsler Full-Scale IQ ($F(1,30) = 12.040$, $P < .002$), Oral and Written Language Scales ($F(1,30) = 33.370$, $P < .0005$), and Peabody Picture Vocabulary Test ($F(1,30) = 17.235$, $P < .0005$). Individual subgroups were examined on all cognitive variables, and the subgroups were significantly different on every measure: Wechsler Verbal IQ ($F(4,27) = 6.690$, $P < .001$), Wechlser Performance IQ ($F(4,27) = 10.331$, $P < .001$), Wechlser Full-Scale IQ ($F(4,27) = 10.317$, $P < .001$), Oral and Written Language Scales ($F(4,27) = 12.671$, $P < .0005$), and Peabody Picture Vocabulary Test ($F(4,27) = 9.068$, $P < .001$). Therefore, the cutoff of a standard score of ≥ 90 was sufficient to show a significant difference on every cognitive and language measure for all five subtypes.

Although the subgroups are too small to draw specific conclusions about the nature of each subtype, this analysis does give support to the theory that these subtypes are behaviorally different and that this subtyping method could provide us with more homogeneous cohorts in dyslexia research. Therefore, an analysis of the neuroanatomy across and within subgroups was undertaken as a pilot study to see whether underlying anomalies associated with specific subtypes of readers would be revealed.

Anatomic Results for Subgroups of Dyslexic and Control Subjects

Even though significant results were found, classifying the cohorts into subgroups reduced the number in some of the groups to an untenable size (although some of the larger subgroups still had a number consistent with previous research). Although we cannot draw conclusions from these significant results, the following findings about the subgroups warrant continuation of this study with a greater number of subjects and suggest to researchers that subtyping according to reading deficits might reveal heretofore unseen differences in the neuroanatomy of subtypes of dyslexia.

To determine whether diagnostic subgroups varied on asymmetry, the five subgroups were compared via multivariate ANOVA on asymmetry quotients and significant differences were found ($P = .043$). Because there was a significant subgroup difference at the multivariate but not the univariate analysis, it is possible that, owing to the small numbers in some subgroups, there was not enough power to be statistically significant at the univariate level. These results are depicted in Figure 2.

Table 3. Mean Standard Scores (SD) for Groups on Cognitive and Behavioral Measures

Group	*Subgroup*	*FSIQ*	*VIQ*	*PIQ*	*OWLS*	*PPVT*
Controls	C (n = 12)	110.92 (9.34)	111.15 (10.34)	108.31 (10.14)	106.15 (11.10)	114.23 (13.36)
	WPC (n = 4)	96.75 (15.65)	96.75 (13.94)	96.50 (14.53)	94.75 (12.10)	99.25 (11.03)
	Totals (n =16)	107.59 (12.24)	107.76 12.50)	105.53 (11.97)	103.47 (12.02)	110.71 (14.13)
Dyslexics	PDD (n = 10)	95.73 (10.10)	93.64 (11.28)	98.73 (09.88)	82.00 (11.66)	94.36 (09.76)
	NDD (n = 3)	101.33 (04.04)	104.67 (07.77)	96.67 (00.58)	83.00 (04.36)	94.00 (09.54)
	GDD (n = 3)	71.67 (01.16)	79.33 (06.81)	68.00 (04.58)	66.67 (04.04)	73.33 (09.07)
	Totals (n = 16)	92.47 (13.01)	93.06 (12.40)	92.94 (14.35)	79.47 (11.27)	90.59 (12.21)

C = strict controls; FSIQ = Wechsler Full-Scale IQ; GDD = global deficit dyslexics; NDD = nonphonologic deficit dyslexics; PDD = phonologic deficit dyslexics; PIQ = Wechsler Performance IQ; OWLS = Oral and Written Language Scales; PPVT = Peabody Picture Vocabulary Test; VIQ = Wechsler Verbal IQ; WPC = weak phonologic controls.

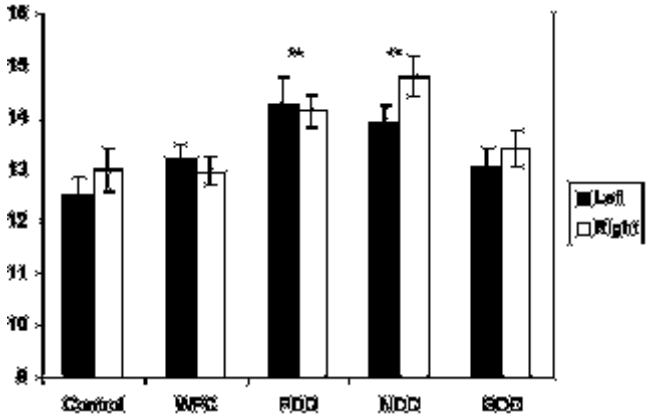

Figure 2. Total prefrontal cortex volume (percent total brain volume) across subgroups. C = strict controls; GDD = global deficit dyslexics; NDD = nonphonologic deficit dyslexics; PDD = phonologic deficit dyslexics; WPC = weak phonologic controls.

An examination of the means and direction of asymmetry quotients in the five subgroups reveals that strict controls had the expected typical rightward prefrontal (mean −0.042, SD 0.165) and leftward occipital (mean +0.023, SD 0.74) asymmetry. The weak phonologic controls showed an atypical leftward prefrontal asymmetry (mean +0.035, SD 0.030) and a typical leftward occipital (+0.033) asymmetry. The phonologic deficit dyslexic subjects had atypical symmetric prefrontal (mean +0.0081, SD 0.152) and symmetric occipital (mean +0.005, SD 0.102) lobe measures. The nonphonologic deficit dyslexic and global deficit dyslexic subgroups had typical prefrontal (rightward) and typical occipital (leftward) asymmetries. Thus, only the phonologic deficit groups (weak phonologic controls, phonologic deficit dyslexic subjects) had atypical asymmetry patterns.

To learn whether prefrontal and occipital lobe volumes differed between subgroups, a two-way repeated-measures multivariate ANOVA was used to evaluate the effect of subgroup (control, weak phonologic dyslexic, phonologic deficit dyslexic, nonphonologic deficit dyslexic, global deficit dyslexic) on volume (total prefrontal, superior prefrontal, inferior prefrontal, total occipital, superior occipital, inferior occipital), with hemisphere (left, right) as the repeated measure and subgroup as the independent variable. No significant differences in overall hemisphere volumes were found, that is, the total left and right hemisphere and total brain volumes did not differ between the subgroups.

A multivariate ANOVA was performed to investigate the lobar volumes in diagnostic subgroups. Whereas no significant differences were found at the multivariate level, significant differences were found at the univariate level. An ANOVA was performed for each subgroup, and the results showed that controls differed significantly from the phonologic deficit dyslexic subjects ($P = .003$) and from the nonphonologic deficit dyslexic subjects ($P = .024$). Total prefrontal volume was larger in both the phonologic deficit dyslexic subjects (left being 14.23% larger than controls and right being 14.14% larger than controls) and the nonphonologic deficit dyslexic subjects (left being 13.93% larger than controls and right being 14.80% larger than controls). The subgroup of good readers (compensated dyslexic subjects, ie, weak phonologic controls) and the subgroup with the global deficits (who are probably not actually dyslexic per se) did not differ from controls.

Anatomic and Behavioral Analysis Results

Pearson correlations were performed to investigate whether any relationships existed between behavioral measures (word attack, word identification, passage comprehension, Oral and Written Language Scales, Peabody Picture Vocabulary Test) and total prefrontal and total occipital volumes or asymmetry quotients. A significant relationship between the total occipital volume and word identification (orthography) performance was found ($R = .452$, $P = .045$). The relationship indicated that the larger the total occipital volume, the better the word identification score and vice versa. The word identification score measures the subject's ability to pronounce regular words that a reader would have acquired as part of a sight vocabulary according to age and grade norms, that is, the reader's lexicon. This word list increased in difficulty; therefore, difficulty could reflect inexperience in reading rather than any specific impairment to an orthographic pathway or working memory.

DISCUSSION

Approximately 70% of the general population (without consideration of handedness) has a right greater than left frontal lobe protruberance (leftward frontal asymmetry) and a left greater than right occipital lobe protruberance (rightward occipital asymmetry). Deviations from these typical asymmetry patterns have been hypothesized as associated with developmental language disorders.[11–17] In the current study, we were interested in examining these lobar asymmetries in a group of adult dyslexic and control subjects and in subgroups defined by specific reading deficits.

Given that anomalous prefrontal asymmetry was seen in dyslexic subjects in an earlier study,[15] it was predicted that dyslexic subjects would have anomalous prefrontal asymmetries. Occipital lobe asymmetries might be related to planum temporale asymmetry,[13] and atypical planum temporale asymmetry has been found in some individuals with dyslexia. Therefore, it was hypothesized that the dyslexic subjects would also have anomalous occipital lobe asymmetry. When asymmetries were examined in dyslexic and control subjects, there were no significant group differences. However, when subgroups were analyzed, the weak phonologic controls and the phonologic deficit dyslexic subjects had anomalous prefrontal (leftward) asymmetry compared with controls (rightward asymmetry). In contrast, both the nonphonologic deficit dyslexic and global deficit dyslexic subgroups had the expected rightward prefrontal asymmetry. These data support Leonard et al's hypothesis that heterogeneous dyslexic cohorts can obscure group differences.[23] An analysis of dyslexia subgroups is important and might identify biologic subgroups that differ on behavioral and anatomic measures. In addition, these data support our hypothesis that including global deficit dyslexic and nonphonologic deficit dyslexic subjects in our analysis of the asymmetry quotients of "dyslexic subjects" could have obscured the anomalous asymmetry of the phonologic subgroups. It is not

surprising to us that both the nonphonologic deficit dyslexic and global deficit dyslexic subgroups had the typical rightward prefrontal asymmetry. These groups might be poor readers owing to inexperience, to other cognitive factors unrelated to neuroanatomy, or to atypical neuroanatomy in other brain regions. A phonologic deficit can be associated with anomalous prefrontal lobar anatomy. The finding that the phonologic deficit dyslexic subjects showed more reversed prefrontal measures than controls is also consistent with the Leonard et al study, which found that a reading-disabled cohort with a phonologic deficit had a marked atypical rightward asymmetry of the cerebral hemispheres.[37]

Only the phonologic deficit dyslexic subjects showed anomalous occipital asymmetry, with more subjects than expected showing symmetry. The weak phonologic controls did not show atypical anatomy in the occipital region, as they did in the prefrontal region. Although speculative, it could be that typical occipital anatomy might enable those individuals with subtle phonologic impairment to compensate. These results also offer support for the Duara et al study, which found atypical asymmetry in the occipital region in dyslexic subjects,[16] and the Haslam et al study, which found more symmetric or atypical occipital widths in dyslexic compared with control subjects.[12]

In addition to the different asymmetry patterns among subgroups, we found significantly larger prefrontal and superior prefrontal volumes in dyslexic subjects compared with controls, although total brain volume did not differ between the groups. Examination of the subgroups revealed that the phonologic deficit dyslexic and the nonphonologic deficit dyslexic subgroups accounted for this difference. Although speculative, it could be that the larger volumes are not related to phonology but to a processing or strategy difference. If a difference between phonologic dyslexic subjects who compensate (weak phonologic controls) and those who do not (phonologic deficit dyslexic subjects) is their ability to add words to their lexicon, then larger prefrontal volumes might be associated with a less efficient ability to access their lexicon.

The finding that the superior prefrontal subregion of the total prefrontal region was driving the significant effect might have functional significance. The superior prefrontal region includes the dorsolateral prefrontal cortex, a structure known to be involved in working memory. This anatomic difference might reflect strength or bias in processing strategies in that dyslexic subjects might rely more heavily on frontal processing strategies than on posterior processing strategies. The greater volume of prefrontal cortex in dyslexic subjects might mean that dyslexic subjects rely on working memory to a greater degree than other processes when reading. Another possibility is that the underlying cellular cortical organization is different in dyslexic subjects. Differences in the numbers of neurons or cell death or proliferation might be associated with these volume differences (see Rosen[38]). Because the superior prefrontal region is one of the last regions of the brain to develop prenatally, this region can be subjected to more insult from prenatal exposure to toxins, viruses, and hormonal influences. In addition, the prefrontal brain regions myelinate late in development, with some evidence that interhemispheric (posterior to frontal) white-matter pathways continue to myelinate into the third decade. These factors can contribute to anomalous or compensatory mechanisms that negatively impact language functions. Although only approaching significance, the results indicate that dyslexic subjects do show somewhat smaller total occipital volumes than controls. The mismatch in volume between posterior and frontal brain regions in the dyslexic subjects (smaller occipital volumes, larger prefrontal volumes) could induce anomalous inter- and intrahemispheric connections, and these anatomic anomalies could represent a neural risk for reading disorders.

The final question addressed in this study was whether any differences in these measures between dyslexic and control subjects, or subgroups, correlate with their performance on cognitive and behavioral measures. The finding that the phonologic deficit dyslexic subjects also showed lower mean Wechsler Verbal IQ scores than controls and all but the global deficit dyslexic group (probably not actually dyslexic) is consistent with the results from the Hier et al study, which found lower mean Wechsler Verbal IQ scores associated with reversed occipital lobe asymmetry in dyslexic subjects.[11] Hier et al speculated that this configuration might reflect atypical cerebral laterality that could weaken or impair language functions. It could be that this configuration actually impairs the ability to compensate.

The finding that the weak phonologic controls were significantly different from controls on IQ measures but not significantly different from the phonologic deficit dyslexic subjects offers support for this group as behaviorally distinct from controls. It supports our decision to separate them from strict controls and to hypothesize that they are compensated dyslexic subjects. Although they were able to compensate and perform well on measures of orthography and semantics, the phonologic deficit dyslexic subjects, from whom they did not differ on IQ measures, were not able to compensate to the same degree. The question remains of how the weak phonologic controls differ from those who apparently are not able to compensate. The weak phonologic controls were the only group that did not differ from controls on the measure of listening comprehension. If the weak phonologic control group does, indeed, represent compensated dyslexic subjects, it could be that the compensatory measures they have developed (listening, semantics, syntax) enabled them to compensate on this measure. The finding that in the total occipital region the phonologic deficit dyslexic subjects have more symmetry, rather than the typical leftward asymmetry, although not statistically significant, might reflect phonologic dyslexic subjects' difficulty in auditory processing.

A significant relationship between the left total occipital volume and word identification (sight vocabulary, ie, lexicon) performance indicated that the larger the total occipital volume, the better the word identification score and vice versa. Some information that could elucidate this finding comes from two studies of patients following stroke with anomic aphasia (pure naming problems). In both studies, the patients had lesions to posterior left hemisphere brain regions (ventral temporal lobe). In the first study, a patient had a discrete stroke in Brodmann's area 37, an area containing the middle and inferior temporal gyri extending onto the ventral surface of the brain.[39] As a result of the stroke, the patient had a naming disorder with preserved semantic knowledge. The patient could not access the word from his or her lexicon in any output modality. This lexical output

deficit was beyond semantic knowledge and was a problem with multimodal lexical access. In the second study, two patients with anomic aphasia had lesions in Brodmann's areas 37 and 6 (ventral and temporal lobes) within the network involved in accessing names.[40] Brodmann'a area 37 is included in the total occipital region of interest in this study. Evidence from the stroke studies indicates that naming can be disrupted from a lesion to a portion of this discrete brain region. It could be that reduced occipital volumes in dyslexic subjects might be associated with increased effort in accessing words from their lexicon or, perhaps, might be associated with a less effective strategy. These dyslexic subjects might rely more on phonologic or semantic processing strategies to read, or, if they fail to use compensatory strategies, their overall reading ability might be impaired. Although this explanation is speculative, it does provide implications for further research, particularly with a combined structure and function study using volumetric and functional MRI.

SUMMARY

Overall, as predicted, dyslexic and control subjects differed in some significant ways, both behaviorally and anatomically. The fact that the phonologic subgroups of dyslexic and control subjects showed some anomalous asymmetry patterns and dyslexic subjects showed larger volumes in the prefrontal area could reflect underlying anatomic differences and offer some support for the hypothesis that atypical cerebral laterality, as represented by anomalous cerebral laterality, might be a risk factor for developmental language disorders such as dyslexia.

In future studies, larger subgroups might reveal more about the nature of these subtypes of dyslexia and the interrelationship of various reading processes (phonologic, orthographic, and semantic) and the mechanisms of compensation and might help behaviorally or anatomically determine more homogeneous groupings to improve research validity, contribute to our clinical understanding of dyslexia, and lead to improved intervention strategies based on subtypes. Follow-up functional studies using functional MRI on some of the same subjects examined in the current study could contribute to a better understanding of the role of the superior prefrontal cortex in dyslexia.

Acknowledgments

The primary author thanks Anne L. Foundas, MD, Department of Psychiatry and Neurology, Tulane University School of Medicine, for her generous contributions of resources, support, guidance, and mentorship throughout this research. Thanks to the staff at Tulane, University Hospital, and Charity Hospital, especially Mrs Ballard and Cathy McKay; Cicely Augustine; the faculty at Delgado Community College and Xavier University for allowing recruitment; and the students from those universities who participated in this research.

References

1. Galaburda AM, Sherman GF, Rosen GD, et al: Developmental dyslexia: Four consecutive patients with cortical anomalies. *Ann Neurol* 1985;18:222–223.
2. Foundas AL: The anatomical basis of language. *Top Lang Disord* 2001;21:1–19.
3. Foundas AL, Leonard CM, Gilmore R, et al: Planum temporale asymmetry and language dominance. *Neuropsychologia* 1994;32: 1225–1231.
4. Foundas AL, Leonard CM, Heilman KM: Morphologic cerebral asymmetries and handedness: The pars triangularis and planum temporale. *Arch Neurol* 1995;52:501–508.
5. Weinberger DR, Luchins DJ, Morihisa J, Wyatt RJ: Asymmetrical volumes of the right and left frontal and occipital regions of the human brain. *Ann Neurol* 1982;11:97–100.
6. Koff E, Naeser MA, Pieniadz JM, et al: Computerized tomographic scan hemispheric asymmetries in right- and left-handed male and female subjects. *Arch Neurol* 1986;43:487–491.
7. LeMay M: Morphological cerebral asymmetries of modern man, fossil man, and nonhuman primate. *Ann N Y Acad Sci* 1976;280: 349–365.
8. LeMay M, Kido DK: Asymmetries of the cerebral hemispheres on computed tomograms. *J Comput Assist Tomogr* 1978;2:471–476.
9. Good CD, Johnsrude IS, Ashburner J, et al: A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 2001;14:21–36.
10. Watkins KE, Paus T, Lerch JP, et al: Structural asymmetries in the human brain: A voxel-based statistical analysis of 142 MRI scans. *Cereb Cortex* 2001;11:868–877.
11. Hier DB, LeMay M, Rosenberger PB, Perlo VP: Developmental dyslexia: Evidence for a subgroup with a reversal of asymmetry. *Arch Neurol* 1978;35:90–92.
12. Haslam RH, Dalby JT, Johns RD, Rademaker AW: Cerebral asymmetry in developmental dyslexia. *Arch Neurol* 1981;38:679–682.
13. Pieniadz JM, Naeser MA: Computed tomographic scan cerebral asymmetries and morphologic brain asymmetries. *Arch Neurol* 1984;41:403–409.
14. Strub RL, Black FW, Naeser MA: Anomalous dominance in sibling stutterers: Evidence from CT scan asymmetries, dichotic listening, neuropsychological testing and handedness. *Brain Lang* 1987;30:338–350.
15. Hynd GW, Semrud-Clikeman M, Lorys AR, et al: Brain morphology in developmental dyslexia and attention deficit disorder/ hyperactivity. *Arch Neurol* 1990;47:919–926.
16. Duara R, Kushch A, Gross-Glenn K: Neuroanatomic differences between dyslexic and normal readers on magnetic resonance imaging scans. *Arch Neurol* 1991;48:410–416.
17. Foundas AL: Is language laterality established by 5 years of age? *Neurology* 2003;60.
18. Orton ST: Introduction: Studies in stuttering. *Arch Neurol Psychiatry* 1927;18:671–672.
19. Geschwind N, Galaburda AM: Cerebral lateralization: Biological mechanisms, associations, and pathology (parts I, II, and III). *Arch Neurol* 1985;42:428–459.
20. Habib M, Robichon F, Levrier O, et al: Diverging asymmetries of temproro-parietal cortical areas: A reappraisal of Geschwind/ Galaburda theory. *Brain* 1995;48:238–258.
21. Hynd GW, Semrud-Clikeman M: Dyslexia and brain morphology. *Psychol Bull* 1989;106:447–482.
22. Filipek PA: Neurobiologic correlates of developmental dyslexia: How do dyslexics' brains differ from those of normal readers? *J Child Neurol* 1995;10(Suppl):S62–S68.
23. Leonard CM, Lombardino LJ, Walsh K, et al: Anatomical risk factors that distinguish dyslexia from SLI predict reading skill in normal children. *J Commun Disord* 2002;35:501–531.
24. Shaywitz BA, Shaywitz SE, Pugh KR, et al: Disruption of posterior brain systems for reading in children with developmental dyslexia. *Biol Psychiatry* 2003;52:101–110.
25. Foundas AL, Angeles V, Bollich AM, et al: Atypical cerebral laterality in adults with persistent developmental stuttering. *Neurology* 2003;61:1378–1385.

26. Dalby MA, Elbro C, Stodkilde-Jorgensen H: Temporal lobe asymmetry and dyslexia: An in vivo study using MRI. *Brain Lang* 1998;62:51–69.
27. Briggs G, Nebes R: Patterns of hand preference in a student population. *Cortex* 1974;11:230–238.
28. Woodcock RW, McGrew KS, Materh N: *WJ III Tests of Cognitive Abilities and Tests of Achievement*, Itasca, IL, Riverside, 2001.
29. Hannah EP: Persistent language/learning disability problems in a college level population., Presented at the annual convention of the American Speech-Language-Hearing Association, New Orleans, LA, 11-12-1987.
30. Stanovich KE: The right and wrong places to look for the cognitive locus of reading disability. *Ann Dyslexia* 1988;38:154–177.
31. Siegel LS: The discrepancy formula: Its use and abuse, in Shapiro BK, Accardo PJ, Capute AJ (eds): *Specific Reading Disability: A View of the Spectrum*, Timonium MD, York Press, 1998, 123–136.
32. Besner D, Smith MC: Basic Processes in Reading: Is the Orthographic Depth Hypothesis Sinking? in Frost R, Katz J (eds): *Orthography, Phonology, Morphology and Meaning*, Amsterdam, Elsevier Science Publishers, 1992.
33. Rasband W: *NIH Image*, 1992;NIH Image is a public domain program developed at the United States National Institutes of Health and available on the Internet at http://rsb.info.nih.gov/nih-image/.
34. Leonard CM, Voeller KKS, Lombardino LJ, et al: Anomalous cerebral structure in dyslexia revealed with magnetic resonance imaging. *Arch Neurol* 1993;50:461–469.
35. Galaburda A: Anatomic basis of cerebral dominance, in Davidson RJ, Hugdahl K (eds): *Brain Asymmetry*, Cambridge, MA, MIT Press, 1995, 51–73.
36. Foundas AL, Lane AB, Corey DM, et al: Anomalous anatomy of speech-language areas in adults with persistent developmental stuttering. *Neurology* 2001;57:207–215.
37. Leonard CM, Eckert MA, Lombardino LJ, et al: Anatomical risk factors for phonological dyslexia. *Cereb Cortex* 2001;11:148–57.
38. Rosen GD: Cellular, morphometric, ontogenetic and connectional substrates of anatomical asymmetry. *Neurosci Biobehav Rev* 1996;20:607–615.
39. Raymer AM, Foundas AL, Maher LM, et al: Cognitive neuropsychological analysis and neuroanatomic correlates in a case of acute anomia. *Brain Lang* 1997;58:137–156.
40. Foundas AL, Daniels SK, Vasterling JL: Anomia: Case studies with lesion localization. *Neurocase* 1998;4:35–43.