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Brain morphometry in reading-disabled twins

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Article abstract—*Objective:* To test for brain structure differences in reading disability (RD) by means of MRI-based morphometry. *Background:* Consensus is lacking on the brain structural correlates of RD. The current study reports on a wider set of structures in the largest sample yet studied, controlling for age, gender, IQ, and attention deficit hyperactivity disorder (ADHD). *Methods:* A case-control study was performed that was comprised of 75 individuals with RD (mean age, 17.43 ± 4.29 years) and 22 control subjects without RD (mean age, 18.69 ± 3.75 years), each a single member of a twin pair. The two groups were similar in age, gender, and handedness, but differed in full-scale IQ (FSIQ), with the RD group having a lower mean FSIQ (101.8 ± 9.9 versus 118.3 ± 10.3). Using three group-by-structure analyses of covariance, groups were compared in terms of volume (in cubic centimeters) of major neocortical subdivisions, subcortical structures, and midsagittal areas (in square millimeters) of three subdivisions of the corpus callosum. *Results:* Controlling for age, gender, and IQ, the authors found a significant group-by-structure interaction for the major neocortical subdivisions ($p = 0.002$), reflecting a different developmental pattern in the RD group, with the insula and anterior superior neocortex being smaller and the retrocallosal cortex being larger in the RD group. In contrast, they found no group main or interaction effects for the subcortical or callosal structures. The pattern of results was essentially the same in subjects without ADHD. *Conclusions:* Most brain structures do not differ in size in RD, but cortical development is altered subtly. This study replicates in a larger sample previous findings of insular differences in RD and demonstrates further that those differences are not attributable to comorbid ADHD. **Key words:** Dyslexia—Reading disability—Brain morphometry—Structural MRI.

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Reading disability (RD) or dyslexia is a common developmental disorder in which the development of reading and spelling skills are disrupted, usually by an underlying phonologic deficit.¹ It affects approximately 3 to 10% of the population, and is nearly equally frequent in men and women, with a male-to-female ratio of approximately 1.5:1.² Genetic influences have been documented in its etiology.³ RD has been linked to genetic markers on the short arm of chromosome 6 in five samples by three independent laboratories, strongly suggesting the existence of a quantitative trait locus affecting RD,^{4–7} although a fourth laboratory using a different phenotype definition did not replicate this result.⁸ There is also evidence for a second genetic locus on chromosome 15, which influences RD.^{5,9} Presumably these and possibly other genes involved in the etiology of RD alter brain development subtly to produce the relatively circumscribed cognitive deficits observed in this disorder. However, we know less about the neurologic phenotype of RD than we know about either its genetic etiology or its cognitive phenotype.

Previous autopsy or MRI studies of brain struc-

ture in RD have examined size differences in the temporal lobe, especially the planum temporale,^{10–14} insula,¹¹ corpus callosum,^{15–19} and thalamus,^{20,21} although no finding for a given structure has been replicated consistently across studies. Moreover, the samples in these studies were small and usually highly selected, and both anatomic definitions and methods of image acquisition varied across studies.²²

In this study we tested for differences in brain structure in RD using quantitative MRI analyses in a relatively large sample of individuals with RD ($n = 75$) and control subjects ($n = 22$) who are single members of twin pairs selected from a large sample of twin pairs with and without RD. The volumes of major cortical and subcortical structures were measured blindly from MR images and tested for group differences.

This study differs from previous studies of brain structure in RD in that it has the largest sample yet studied and analyzes a wider set of structures. Because brain size is known to be related to age, gender, and IQ, it is important to control for those sources of variation. RD is also known to be comorbid

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with attention deficit hyperactivity disorder (ADHD), so it is also important to control for that potential confound. Most existing studies of brain structure in RD have focused on a few localized structures, and have rarely controlled all these other sources of variation, so it remains unclear whether there are brain structure differences specific to RD, and, if there are such differences, how widespread they are.

Methods. Patients and control subjects. Colorado Learning Disability Research Center (CLDRC) twin sample. The research presented here is part of the CLDRC study,²³ in which a large sample of twins with RD and control twins are being studied at genetic, neurologic, and cognitive levels of analysis. The MRI subsample of RD and control twin pairs are recruited from the larger population sample of twins who have already participated in other studies of the CLDRC.²³ To minimize the possibility of referral bias,²⁴ CLDRC twin pairs are ascertained systematically through 27 cooperating school districts within the state of Colorado. Without regard to reading status, all twin pairs within each district are identified, and permission is then sought from parents to review the school records of both members of each pair for evidence of reading problems. If either member of a twin pair manifests a positive history of reading problems (e.g., low reading achievement test scores, referral to a reading therapist because of poor reading performance, reports by classroom teachers or school psychologists, etc.), both members of the pair are invited to complete an extensive battery of tests in the laboratories of the CLDRC.

A comparison group of control twin pairs is also recruited who are matched to probands on the basis of age, gender, and school district. In order for a twin pair to be included in the control sample, both members of the pair must have a negative school history for reading problems and must be classified as unaffected by psychometric testing.

All twins are administered a psychometric test battery that includes the Wechsler Intelligence Scale for Children–Revised²⁵ (WISC-R) or the Wechsler Adult Intelligence Scale–Revised²⁶ (WAIS-R) and the Peabody Individual Achievement Test²⁷ (PIAT). Employing discriminant weights estimated from an analysis of PIAT reading recognition, reading comprehension, and spelling data obtained from an independent sample of nontwin children, 140 with histories of reading problems and 140 without such histories,²⁸ a discriminant function score (“reading composite score”) is then computed for each subject. In order for an individual to be diagnosed as being reading disabled, he or she must have a positive school history for reading problems and must also be classified as affected by the discriminant score, which is an age-discrepancy criterion for RD. Additional diagnostic criteria include an IQ score of at least 90 on either the verbal or performance scale of the WISC-R or WAIS-R, no evidence of neurologic problems, and no uncorrected visual or auditory acuity deficits. Children with major psychiatric problems were also excluded.

Selected items from the Nichols and Bilbro²⁹ questionnaire are used to determine zygosity of twin pairs. In ambiguous cases, zygosity of the pair is confirmed by standard genotyping analysis of blood samples. In the RD proband cohort, a total of 198 pairs of identical (monozy-

Table 1 Description of the cohort

Variable	RD subject	Control subject
n	75	22
M/F	40/35	11/11
MZ/DZ	40/35	11/11
Age at MRI, y (SD)	17.43 (4.29)	18.69 (3.75)
FSIQ, score (SD)	101.76 (9.88)	118.32* (10.34)
Reading composite, score (SD)	-1.16 (0.67)	1.80* (0.68)
Handedness quotient,† score (SD)	1.19 (0.27)	1.07 (0.10)

* $p < 0.001$.

† Handedness quotient determined by using the Oldfield Handedness Inventory: 11 items; score 1 for right-hand performance, 2 for left-hand performance; quotient = total score/11.

RD = reading-disabled; MZ = monozygotic; DZ = dizygotic; FSIQ = full-scale IQ.

gotic [MZ]) twins, 148 pairs of same-sex fraternal (dizygotic [DZ]) twins, and 97 pairs of opposite-sex DZ twins meet criteria for inclusion (i.e., at least one member of the pair of twins is reading disabled). In addition, a total of 157 pairs of MZ twins and 107 pairs of same-sex DZ twins comprise the current CLDRC control sample. These twins are all being reared in English-speaking, middle-class homes.

MRI twin sample. The MRI project is approved by the institutional review board of the University of Colorado. For individuals who agree to participate, the nature of the study and the MRI procedure is explained verbally to the participants and their parents. They then read and sign a written consent form, and are paid \$50 for their participation. The following selection criteria are used to select same-sex twin pairs for the MRI study from the larger CLDRC twin sample: 1) 12 years of age or older and 2) sex and ethnicity representative of the overall sample.

The individuals in the current study came from 75 twin pairs in which at least one member of the pair has RD, and from 22 twin pairs in which neither member has RD. To avoid the problem of statistically dependent data, one member from each pair was selected randomly for the current analyses, which compared 75 unrelated individuals with RD to 22 unrelated control subjects. As can be seen in table 1, both the RD and the control groups have similar proportions from MZ and DZ pairs. The RD and the control groups are also similar in gender and age at the time of MRI.

Handedness is measured by an 11-item questionnaire regarding hand preference for everyday activities (e.g., write, throw, and hammer). For each item, a right-hand preference is scored as a 1 and a left-hand preference is scored as a 2. The handedness score is the average score across the 11 items, ranging from 1.0 (exclusively right-handed) to 2.0 (exclusively left-handed). As can be seen in table 1, the mean handedness scores do not differ by group.

ADHD is not an excluded condition, and a parent report measure of the symptoms of ADHD (the parent form of the Diagnostic Interview for Children and Adolescents [DICA ADHD module]) is available for a majority subset ($n = 74$) of the sample. In that subset, 18% ($n = 13$) of the RD

group meet criteria for ADHD (eight or more DICA items reported as positive), as do 4% ($n = 3$) of control subjects, consistent with the well-documented comorbidity between RD and ADHD. To test whether any RD group differences in brain structure are a function of comorbid ADHD, subjects meeting criteria for ADHD were excluded from the subset with ADHD data, and the main analyses were repeated.

MRI acquisition and morphometric procedures. MR image acquisition. All MR images are acquired on the General Electric 1.5-T Signa MR System (5x) (Milwaukee, WI) located at the University of Colorado Health Sciences Center. After standard sagittal scout and coronal T2-weighted sequences, a coronal T1-weighted, three-dimensional (3D) spoiled gradient echo (SPGR) pulse sequence is performed with the following parameters: repetition time, 40 msec; echo time, 8 msec; flip angle, 40 deg; field of view, 24 cm; slice thickness, contiguous 3.0 mm; matrix, 256×256 ; averages, 1; imaging time, 10.5 minutes. All 107 MR images in the current analyses were read clinically as within normal limits.

Positional normalization and image segmentation. All 3D SPGR scans are analyzed blind to diagnosis or twin/sibling status according to a standard morphometric protocol, which includes positional normalization, image segmentation, and partitioning into hemispheric "pericallosal" regions. On each normalized T1-weighted 3D MRI slice, anatomic segmentation is performed using intensity contour mapping and differential intensity contour algorithms, which identify, classify, and create a continuous outline corresponding only to those voxel locations constituting the specified anatomic borders. These algorithms are described in greater detail elsewhere.³⁰⁻³⁵

Global structural measures. For the current study, seven global measures are used, including cerebral cortex, white matter, ventricular system, hippocampus, basal ganglia (sum of caudate and lenticulate volumes), and central gray nuclei (including thalamus; see Filipek et al.³¹ for definitions). The corpus callosum is also defined on the 1-mm midline sagittal slice, superiorly by the sulcus of the corpus callosum, inferiorly by the superior borders of the lateral ventricles, and the anteroposterior extent by the genu and splenium. Seven subdivisions of the corpus callosum are measured using the method of Witelson.³⁶ Subdivisions are combined to yield an anterior, middle, and posterior callosum, representing Witelson's regions 1 through 3, 4 and 5, and 6 and 7 respectively.³⁶

Regional neocortical divisions. The cerebral hemispheres are partitioned into eight subdivisions based on the hemispheric "pericallosal" regional segmentation methods.³⁵ Precallosal (prefrontal) and retrocallosal (posterior parietal/occipital) regions include those slices anterior and posterior to the corpus callosum respectively. The pericallosal region contains the coronal slices surrounding the corpus callosum in continuum, and is divided into anterior pericallosal, anterior to and not including the anterior commissures, and posterior pericallosal, posterior to and including the anterior commissure. The anterior and posterior pericallosal regions are further divided into superior, inferior, and temporal regions by hand-drawn lines connecting the Sylvian fissure, superior circular insular sulcus, and the superolateral lateral ventricle; and the

Sylvian fissure, inferior circular insular sulcus, and optic tract/amygdala/hippocampus.

The cerebral cortex localized within each of these hemispheric regions is subsequently defined. The cortex in the precallosal, anterosuperior, posterosuperior, and retrocallosal regions defines these four neocortical regions. The cortex in the anterior and posterior temporal regions is combined to create the temporal neocortex. Operculum is then defined as the combined cortex located within the anterosuperior and the posterosuperior regions extending from the tip of the superior circular insular sulcus laterally to the external border of the hemisphere. Insula is defined as the combined cortex located within the anteroinferior and posteroinferior regions extending from the tip of the superior to the tip of the inferior circular sulci.

Volumetric and area calculations. Volume (in cubic centimeters) is the dependent measure for all structures except the corpus callosum, with a cross-sectional area that is measured. The total number of voxels for each global structure, and the cortex within each hemispheric neocortical region, is multiplied by the absolute volume of each voxel,^{31,33,34} which is determined by the imaging parameters. The area of the corpus callosum and its subdivisions is measured in square millimeters and calculated similarly. A minimum estimate of the interrater reliability of these morphometric measures is provided by the intraclass correlations within MZ pairs. These range between 0.63 to 0.94 (median, 0.75) for the neocortical measures and between 0.64 and 0.94 (median, 0.73) for the subcortical structures, indicating adequate reliability.

Statistical analyses. Preliminary analyses. Preliminary analyses concern IQ, age, gender, and hemisphere. Because there were group differences in IQ and significant correlations between IQ and many of the structures considered here, we wanted to control for IQ variance in the main analyses. However, this is not a straightforward issue because differences in reading-related cognitive processes or in reading experience may cause IQ differences. In this case, covarying IQ may eliminate brain structure differences that are actually related to RD. For this reason we ran the main analyses both with and without covariance adjustment for full-scale IQ (FSIQ).

We also examined group-by-gender and group-by-hemisphere interactions, none of which were significant. Consequently, neither hemisphere nor gender were retained as variables in the main analyses.

We did find a significant difference between male and female participants for total cerebral volume ($F[1,95] = 45.50$, $p < 0.001$). The mean for male subjects (mean, 1,295.22 mL; SD, 105.42 mL) was significantly larger than the mean for female subjects (mean, 1,146.28 mL; SD, 111.96 mL). Hence, the value in female subjects is approximately 11% smaller than the value in male subjects, which is congruent with earlier reports in normal young adults.³¹ There was a significant gender difference of approximately this magnitude for all the individual brain structures considered here. So clearly there is substantial gender variance in structure size, and thus the question arises as to how to control this gender variance when testing for the likely smaller effects of RD status on structure size. Including gender along with RD group as an independent variable in the main analyses greatly reduces the power to detect main or interaction effects of group, so we

adopted another method of controlling for gender variance. We separated the total twin sample into male subjects and female subjects, and calculated gender-specific z scores for each individual for each structure examined here. Thus, if a male subject and a female subject were both at the mean for their gender in the size of a given structure, they would each get a z score of zero, even though the raw volume for the male subject is larger than that for the female subject. We then merged the data files for male subjects and female subjects, and randomly selected one individual from each twin pair to create the sample of 75 individuals with RD and 22 control subjects. Both the RD and the control groups contain male subjects and female subjects (see table 1), but gender variance in structure size has been removed from the data.

The final covariance issue concerned age. Age is correlated with structure size in this and other MRI data sets. In an earlier study of RD brain morphometry,¹³ covarying age eliminated many of the previously significant group differences. Thus we also examined whether covarying age altered our results.

Main analyses. We tested for RD versus control group differences in three analyses: 1) volumes of individual neocortical structures, 2) volumes of individual subcortical structures, and 3) areas of the three divisions of the corpus callosum. These analyses used group-by-structure mixed-model analyses of covariance (ANCOVAs; covarying age and FSIQ). Analyses of single variables, to test for simple effects, were performed using one-way ANCOVAs (again, covarying age and FSIQ).

Ancillary analyses. All results were then retested with ADHD subjects excluded, again using three group-by-structure mixed-model ANCOVAs (covarying age and FSIQ).

Results. Group characteristics. As already mentioned, the RD (n = 75) and the control (n = 22) groups were similar in zygosity, age at the time of MRI, gender ratio, and handedness scores (see table 1). Because RD and control pairs were selected to be different on their reading composite scores, not surprisingly there is a highly significant difference ($p < 0.001$) between the two groups in terms of this variable. The control subjects are approximately 3 SDs higher than RD subjects on this reading composite score. Because the reading composite score correlates moderately with FSIQ ($r = 0.60$, $p < 0.001$), there was also a significant FSIQ difference between the two groups ($F[1,95] = 46.79$, $p < 0.001$). However, the mean FSIQ for each group is at least the population average (100) or higher, and the FSIQ difference between the RD subjects and the control subjects (approximately 1 SD) is much smaller than their difference in reading composite scores. So, this RD group, which is defined as RD because of reading performance below age level, is also reading well below FSIQ level.

Main analyses. We present our results in the following order: neocortical structures, subcortical structures, and divisions of the corpus callosum.

The mixed-model ANCOVA (covarying age and IQ) for the gender-corrected values of the seven neocortical regions found a significant group-by-structure interaction effect ($F[6,546] = 3.46$, $p = 0.002$), but no main effect of group. Thus, although there is not an overall group difference in neocortical volume, there are group differences for

Table 2 Means (SDs) for volumes of neocortical and subcortical structures by group

Structure	Reading-disabled subjects	Control subjects
Neocortical, cm ³		
Precallosal	121.53 (19.05)	121.28 (17.25)
Anterior superior	74.81 (16.25)	80.24 (13.94)
Posterior superior	126.89 (25.83)	124.01 (20.62)
Insula	19.42 (2.33)	21.15 (2.90)
Temporal	106.24 (15.97)	105.21 (15.93)
Opercular	27.15 (5.30)	27.82 (4.54)
Retrocallosal	246.70 (39.08)	243.09 (31.16)
Subcortical, cm ³		
White matter	412.25 (69.00)	430.26 (59.61)
Total ventricles	17.24 (7.10)	17.50 (8.47)
Basal ganglia	24.05 (3.22)	24.12 (3.37)
Hippocampus	7.46 (1.75)	7.35 (1.79)
Central gray	25.43 (2.49)	26.06 (2.23)
Callosal, mm ²		
Anterior	252.56 (42.66)	254.63 (39.75)
Middle	133.20 (21.18)	139.65 (17.42)
Posterior	193.83 (36.29)	211.42 (39.84)

specific neocortical regions. The interaction arises because the pattern of adjusted means across the seven neocortical regions varies by group. The RD group has a significantly smaller anterior superior neocortex (mean \pm SEM, -0.115 ± 0.115 cm³ versus 0.579 ± 0.240 cm³; $p = 0.02$) and a trend toward a significantly smaller insula (-0.073 ± 0.111 cm³ versus 0.436 ± 0.232 cm³, $p = 0.07$). In contrast, the adjusted mean in the RD group is larger, though not significantly so, for retrocallosal neocortex (0.119 ± 0.108 cm³ versus -0.216 ± 0.226 cm³). The same pattern of results is evident in the raw means in table 2, but in this case only the insula difference (RD group smaller) is significant ($p = 0.005$).

This group-by-structure interaction effect is robust across different adjustments of the data. It is found if we repeat the ANCOVA (age and IQ covaried) using raw volumes instead of gender-corrected scores ($F[6,546] = 3.01$, $p = 0.007$), so it does not depend on the use of gender-corrected scores. It is also found in the gender-corrected scores regardless of whether age or IQ is covaried (F value range, 2.91 to 3.18; p value range, 0.004 to 0.008), but it is not found in the raw data with no covariates or only age covaried. Therefore, the interaction does depend on controlling other sources of variation, especially those related to gender and IQ. Across these various analyses, the pattern of the RD group being smaller for some structures (insula and anterior superior neocortex) and larger for others (usually retrocallosal cortex) is maintained, although which individual structures are significantly different between groups varies.

In contrast to these significant results for neocortical regions, the mixed-model ANCOVA (covarying age and IQ) for the gender-corrected values of the five individual sub-

cortical structures found neither a main effect of group nor a significant group-by-structure interaction effect ($F < 1.0$; not significant). As can be seen in table 2, the means for each of the five structures are similar in the two groups. The same null results were found in the raw score analyses, regardless of what was covaried.

The final level of analysis concerned the corpus callosum. The mixed-model ANCOVA (covarying age and IQ) of the gender-corrected values of the three divisions of the corpus callosum found neither a main effect of group ($F < 1.0$; not significant) nor a group-by-division interaction ($F[2,91] = 1.66, p = 0.19$). The same null results were found in the raw score analyses, regardless of what was covaried. Inspection of table 2 reveals that the means for the areas of the anterior and middle division are similar in the two groups, whereas for the posterior division the RD mean is approximately 0.5 SD smaller than the control mean—a difference that is only marginally significant ($p = 0.054$). However, this trend is not present in the adjusted means from the main analysis, and may represent a chance finding.

Ancillary analyses. We next tested whether these results would be maintained in the sample restricted to subjects without ADHD. As mentioned earlier, when the sample was restricted to subjects without ADHD, there were 43 subjects with RD and 15 control subjects. The three ANCOVAs (covarying age and IQ) examining gender-controlled values for the neocortical, subcortical, and callosal structures were repeated with these non-ADHD subgroups. The neocortical ANCOVA found a significant group-by-structure interaction effect ($F[6,318] = 3.13, p = 0.005$). Consistent with the results in the full sample, this interaction arises because the RD group is smaller for some structures and larger for others. Specifically, follow-up analyses of the adjusted means found a trend ($-0.073 \pm 0.140 \text{ cm}^3$ versus $0.534 \pm 0.254 \text{ cm}^3, p = 0.087$) toward a smaller insula in the RD group in contrast to a significantly larger ($0.288 \pm 0.142 \text{ cm}^3$ versus $-0.341 \pm 0.257 \text{ cm}^3, p = 0.025$) retrocallosal cortex in the RD group. The earlier finding of a significantly smaller anterior superior neocortex in the RD group was not maintained in this subgroup analysis, although the adjusted means ($-0.008 \pm 0.146 \text{ cm}^3$ versus $0.533 \pm 0.264 \text{ cm}^3$) in the subsample were similar to those in the full sample ($-0.115 \pm 0.115 \text{ cm}^3$ versus $0.579 \pm 0.240 \text{ cm}^3$). As can be seen by comparing tables 2 and 3, the mean cortical values for the raw scores for each group change little when the sample is restricted to subjects without ADHD.

The results from the subcortical ANCOVA were also consistent with the results in the total sample. Again, there were no significant main or interaction effects of group ($F < 1$; not significant). Again, comparing tables 2 and 3 reveals little change in the mean subcortical values for each group when the sample is restricted to subjects without ADHD.

Similarly, the results for the callosal ANCOVA remained nonsignificant in the subsample without ADHD. There was neither a significant main or interaction effect of group ($F < 1$; not significant). The mean callosal values of the RD and the control subsamples without ADHD (see table 3) are very similar to those in the total sample (see table 2).

In summary, eliminating subjects with ADHD does not

Table 3 Means (SDs) for measures in subsample without ADHD

Structure	Reading-disabled subjects (n = 43)	Control subjects (n = 15)
Neocortical, cm^3		
Precallosal	122.96 (20.27)	122.53 (18.02)
Anterior superior	75.94 (15.22)	78.02 (13.41)
Posterior superior	128.79 (24.61)	130.82 (17.15)
Insula	19.41 (2.41)	21.43 (3.05)
Temporal	106.77 (17.06)	103.45 (15.63)
Opercular	27.58 (5.95)	27.67 (4.12)
Retrocallosal	251.63 (42.20)	241.15 (33.47)
Subcortical, cm^3		
White matter	398.51 (60.29)	439.36 (67.65)
Total ventricles	15.65 (6.40)	18.49 (9.09)
Basal ganglia	23.74 (3.12)	24.09 (3.47)
Hippocampus	7.12 (1.48)	7.64 (1.96)
Central gray	25.40 (2.29)	26.45 (2.33)
Callosal, mm^2		
Anterior	247.01 (40.19)	261.75 (37.19)
Middle	133.15 (22.94)	142.38 (18.16)
Posterior	193.45 (37.94)	210.67 (43.41)

ADHD = attention-deficit hyperactivity disorder.

change the results, so the group-by-structure interaction for the neocortical divisions is also robust when ADHD is controlled.

Discussion. Using MRI-based morphometry, we tested for brain structure differences in individuals with RD by examining neocortical, subcortical, and callosal subdivisions, and controlling for variance related to gender, age, and IQ. The only positive result was a robust group-by-structure interaction for the neocortical subdivisions, which was attributable to some divisions being smaller in the RD group (insula and anterior superior neocortex) and one division being larger (retrocallosal neocortex). There were no significant results in the analyses of the subcortical and callosal subdivisions. When subjects with ADHD were removed from the sample, the results were quite similar.

This study replicates in a larger sample a previous finding of a smaller size bilaterally of the insula in individuals with RD¹¹ and also converges with the results of a PET study, which found reduced activation of the insula in RD.³⁷ It also demonstrates that the insula differences are not attributable to comorbid ADHD. The functions of the insula have not been well defined, although lesions to the insula have been reported to be associated with aphasic symptoms. A recent comparison of left-hemisphere stroke patients with (n = 25) and without (n = 19) articulatory planning deficits found the left precentral gyrus of the insula was consistently damaged in the former

group and consistently spared in the latter, supporting the hypothesis that this portion of the insula is important for the motor planning of speech.³⁸ This finding is interesting given that developmental articulation disorder is both comorbid and cofamilial with RD,³⁹ although the brain bases of developmental articulation disorder are not well understood.

Volume differences in anterior superior and retrocallosal neocortex have not been identified in previous MRI studies of RD, so these findings await replication. Anterior superior neocortex includes Broca's area, so there is a potential theoretical basis for this association.

We did not find clear evidence of callosal differences in RD. A role for the corpus callosum in RD is consistent with studies of individuals with acquired alexias⁴⁰ and has also been suggested by studies of callosal transfer time in children with RD.⁴¹ Although a case can be made for the relevance of the corpus callosum to RD, the results of previous MRI studies of this structure in RD are remarkably inconsistent. For instance, Hynd et al.¹⁶ found their dyslexic group, unlike ours, had a smaller anterior portion of the corpus callosum. Rumsey et al.¹⁸ found a selectively larger posterior callosum—a result directly opposite to the trend found here. Hence, more research is needed to clarify whether there are callosal differences in RD.

An important issue raised by this study is the need to control for other, often larger sources of variation (such as gender) when seeking to identify the brain morphometric correlates of developmental disorders. Even with this relatively large sample, detecting robust differences depended on whether these other sources of variation, especially gender and IQ, were controlled. Earlier MRI studies of RD have had smaller samples, and differed in whether they controlled variance related to gender, age, IQ, and ADHD. Hence, some of the inconsistency of the results across studies is likely due to these methodological differences.

The discriminant validity of the brain structure correlates of RD identified here can be evaluated by comparing them with the brain structure correlates of other individual differences. In general, the brain structural differences in RD found here are smaller and more subtle than the brain correlates of more severe developmental disorders, such as Down⁴² and Fragile X syndromes,⁴³ in which overall brain size is affected. The brain correlates of RD identified here also mostly differ from those found for ADHD³⁵; these include basal ganglia, frontal, and parietal differences. We also demonstrated that our results were not due to comorbid ADHD. Lastly, they also differ from the brain correlates of gender and normal IQ variations. As presented earlier, there is a very robust gender difference in total cerebral volume in this sample, with the female volume being 11% smaller than the male volume. This gender difference appears to be a general one because it is present in all of the structures examined here, which

replicates our previous findings in normal control subjects.³¹ Similar gender differences in overall brain size have also been found in autopsy samples.⁴⁴ There is a significant correlation ($r = 0.278$, $p < 0.01$) between total cerebral volume and FSIQ in this sample, which is consistent with earlier studies.⁴⁵ In a separate study of this sample⁴⁶ we found a greater correlation between IQ and subcortical volume than neocortical volume. This pattern contrasts with the current results, in which RD is not related to subcortical volume. In sum, the brain structure correlates of other developmental disorders and of both gender and IQ are different from the brain structure correlates of RD identified here, thus providing evidence for discriminant validity.

Altogether, our results indicate a subtly different pattern of cortical development in individuals with RD, with some language-related regions being smaller and at least one nonlanguage area being larger, suggesting possible developmental tradeoffs or compensations. How this different pattern arises developmentally is the next important question to address. Because this is a twin sample, with more subjects it will be possible to examine the etiologic relation between the few brain differences we found and RD. As stated earlier, RD is known to be heritable. In a separate study we found moderate heritability for total cerebral volume, left and right neocortex, and a composite of subcortical structures.⁴⁶ The next step is to test whether there are shared genetic (or environmental) influences on reading deficits and the different pattern of cortical development found here. This pattern could be a direct effect of the genes that influence RD, or it could be an effect of an environmental difference in RD, such as a difference in language and reading experience.

Thus, as this sample increases in size, we will be able to perform more powerful tests of 1) genetic and environmental covariation between RD and brain structures, 2) brain structure differences between RD subtypes, and 3) symmetry differences in RD, using a finer grained parcellation of the neocortex.

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