

## FAST-TRACK REPORT

# Larger brain and white matter volumes in children with developmental language disorder

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### Abstract

*Developmental language disorder (DLD) is predominantly a language disorder, but children with DLD also manifest non-language impairments, and neuroanatomical abnormalities have been found in multiple areas of the brain, not all language-associated. We therefore performed a whole brain general segmentation analysis of all major brain regions on MRI scans of 24 DLD subjects (16M, 8F) and 30 controls (15M, 15F), ages 5.7 to 11.3 years. Children with DLD showed increased total brain volume, driven predominantly by a substantial increase in the volume of cerebral white matter. Cerebral cortex and caudate were relatively but not absolutely smaller in DLD. These findings are discussed in relation to issues of specificity vs. generality as they arise in debates about (1) modular vs. general processing deficits and connectionist modeling in DLD, (2) language-specific vs. pervasive, non-specific deficits in DLD and (3) specificity of the disorder vs. overlap with other disorders, notably autism.*

### Introduction

Developmental language disorder (DLD) is defined as impairment in language acquisition that may involve language production, comprehension, or both (Bishop, 1992). This language impairment must occur in the setting of normal intelligence, and it may not be explained by other deficits, physical abnormalities or disease processes, or by social or environmental deprivation. DLD is thus a diagnosis of exclusion (Aram, Morris & Hall, 1993).

There is substantial heterogeneity of language phenotype among children who qualify for the DLD diagnosis. In particular, deficits in expressive language, receptive language, or both, and problems with morphology, syntax, phonology, and lexical and pragmatic skills are all seen in varying combinations (Rapin & Allen, 1983; Rapin, Dunn & Allen, 2003). It is also the case that even

though children with DLD are by definition of normal intelligence, the majority exhibit deficits, albeit subtle ones, in multiple other domains, including cognition, emotion and motor performance (Leonard, 1998). Nevertheless, the language disorder is strongly predominant.

The implication of this clinical picture is that DLD is a 'selective' neural systems disorder that mainly involves language mechanisms. While the peri-Sylvian region of the dominant hemisphere is known to be central to language function (Mesulam, 1990; Price, 2000), neuroanatomic analyses undertaken to date have disclosed only a reduction in the degree of hemispheric asymmetry in language-related regions (Jernigan, Hesselink, Sowell & Tallal, 1991) and a tendency toward atypical perisylvian gyral configurations in children with DLD (Clark & Plante, 1998). Moreover, these findings may be absent in subjects with DLD while present in relatives with normal language, so that the focal anatomical correlates identified

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to date are non-deterministic. That is, these anatomical variants are neither necessary nor sufficient for the condition. Some anatomical findings in areas of the brain that are not primarily language-associated, notably the cerebellum (Rae, Karmiloff-Smith, Lee, Dixon, Grant, Blamire, Thompson, Styles & Radda, 1998a; Nicolson, Fawcett & Dean, 2001), have been suggested as correlates of the non-language deficits accompanying the disorder. A voxel-based morphometric analysis of members of the KE family, a well-studied four-generation cohort with a severe language disorder, identified reduced caudate volume that correlated with both language and oral praxis deficits (Watkins, Vargha-Khadem, Ashburner, Passingham, Connelly, Friston, Frackowiak, Mishkin & Gadian, 2002). Others have found abnormalities in non-language areas that remain unexplained from a functional standpoint (Galaburda, Sherman, Rosen, Aboitiz & Geschwind, 1985; Humphreys, Kaufmann & Galaburda, 1990; Rae, Lee, Dixon, Blamire, Thompson, Styles, Talcott, Richardson & Stein, 1998b; Nicolson, Fawcett & Dean, 1999).

Thus, given that the neuroanatomical abnormalities associated to date with language areas are non-deterministic, that there are structural brain abnormalities outside language areas, and that there is a prevalence in children with DLD of more subtle non-linguistic disorders, we need to consider the possibility that anatomic correlates of DLD, if they exist, may not all conform to focal or strictly regional models of cerebral disorders derived from studies of acquired adult language disorders. This suggests a need for whole-brain volumetric surveys of DLD brains that might identify other types of neuroanatomical correlates.

In light of these considerations, this study examines the neuroanatomical findings in DLD subjects more comprehensively. It is possible that the neuroanatomical correlates of a developmental rather than an acquired language disorder may be widespread, involving more than language areas of the brain (Karmiloff-Smith, 1998; Paterson, Brown, Gsodl, Johnson & Karmiloff-Smith, 1999; Leonard, 1998; Bishop, 1998). Such widespread change may disrupt brain function in a non-modular, network-related fashion, and yet because of network dynamics may eventuate in focal-appearing functional deficits (Plunkett, Karmiloff-Smith, Bates, Elman & Johnson, 1997). It is also conceivable that these neuroanatomical alterations may be discernable only in quantitative parameters that are not assessed in standard clinical neuroradiology practice. To consider these possibilities, this study presents a volumetric, whole-brain analysis in which forebrain is partitioned into its principal gray and white matter structures, and compares whole-brain morphometric profiles of children with

DLD to those of controls. While the subjects we profile met criteria for DLD, they also were free of any focal brain pathology, and their MRI scans were judged to be clinically normal by expert neuroradiologists; we thus can address overall morphometric differences in the absence of specific lesions. This morphometric profile demonstrates that there are substantial differences between DLD and control brains even at the level of large-scale segmented brain structures.

## Methods

### Subjects

Quantitative volumetric analysis was performed on brain magnetic resonance images of 31 boys (16 DLD, 15 normal controls) and 23 girls (8 DLD, 15 normal controls) between 7 and 11 years of age (Table 1) (Caviness, Kennedy, Richelme, Rademacher & Filipek, 1996). Mean age at scanning for DLD was 8.3  $\pm$  1.6 years, and for the control subjects it was 9.1  $\pm$  1.2 years. All 24 children with DLD had performance IQs greater than 80. Subjects were accepted into the control group if they had normal school performance and normal neurological examination. DLD children were recruited between 1985 and 1988 by clinical referral or by participation in school special needs programs (Rapin, 1996). The control subjects were recruited specifically to the imaging arm of the study and were eligible if they had normal developmental history without seizures or significant head injury, and if their neurological examinations were normal (Caviness *et al.*, 1996; Bates, Meyer, Makris, Kennedy, Belliveau & Caviness, 1996). English was the primary language of each child's family. Exclusionary criteria included hearing or gross sensorimotor deficits, clinical evidence of progressive encephalopathy, frequent seizures or high doses of anticonvulsant drugs or psychotropic medication, the presence of potentially paramagnetic metals and overtly evident focal brain lesions, brain atrophy or ventriculomegaly. No sedation was used for scanning. Human Subjects Committees at all four participating institutions granted approval, and the parents of all the study children gave written informed consent.

**Table 1** *Subjects*

		Number	Mean age (SD)	Age range
DLD	Female	8	8.17 (1.1)	7.2–10
	Male	16	8.31 (1.8)	5.7–11.3
Control	Female	15	9.13 (1.1)	7.0–11
	Male	15	9.13 (1.3)	6.5–11

**Table 2** Diagnostic variables for children with DLD. NVIQ: nonverbal IQ as assessed by the abstract visual reasoning section of the Stanford-Binet Intelligence Scale, Revised (Thorndike, Hagen & Sattler, 1986); TELD: Test of Early Language Development (Hresko, Reid & Hammill, 1981); MLU: mean length of utterance

	Mean NVIQ (SD)	NVIQ range	Mean TELD (SD)	TELD range	Mean MLU (SD)	MLU range
Female	95.5 (13)	80–110	78.8 (16)	60–102	3.2 (1.1)	1–4
Male	109.2 (20)	85–140	81.8 (10)	67–98	3.5 (1.3)	2–6

### Diagnostic classification

The DLD subjects were recruited before they entered grade school as part of a larger study of children with disorders of language, including autism and low IQ without autism (Rapin, 1996). Children were recruited by either clinical referral for assessment or treatment of communication difficulties, or by solicited participation of schools and programs for special needs children. All children regardless of their diagnoses were screened using the three-part Wing Autistic Disorder Interview Checklist (WADIC) (Rapin, 1996). Children who failed to meet criteria for autism, and whose non-verbal IQ scores, assessed by the abstract visual reasoning section of the Stanford-Binet Intelligence Scale, Revised (Thorndike, Hagen & Sattler, 1986), were above 80, were then screened for DLD. Currently there are no standard criteria for determining the significance of discrepancies in the diagnosis of DLD. In the present study, subjects were given a classification of DLD if in the preschool screening there was significant relative deficiency in language measures, meaning either (a) a standard score on the Test of Early Language Development (TELD) (Hresko, Reid & Hammill, 1981) that was 1 SD below the mean NVIQ score or (b) a mean length of utterance (MLU) score that was 1 SD below the mean for the child's chronological age (Rapin, 1996; Aram *et al.*, 1993). Dunn, Flax, Sliwinski and Aram (1996) have demonstrated that these measures are quite accurate when used to predict a clinical diagnosis of DLD. Means, standard deviations and ranges of NVIQ, TELD and MLU scores for all DLD subjects are presented in Table 2.

### Image acquisition

Magnetic resonance imaging was performed on either General Electric 1.5 T Signa (Milwaukee, WI) or Siemens 1.5 T (Iselin, NJ) magnetic resonance imaging systems. Images were acquired between 1989 and 1992 and included a T1-weighted sagittal scout series, a coronal T2-weighted sequence to rule out overt focal lesions, atrophy or ventriculomegaly, and a coronal volumetric T1-weighted spoiled gradient echo-imaging sequence for the morphometric analysis. When performed on GE

systems, the following parameters were used for the volumetric acquisition: pulse sequence = 3D-SPGR or 3D-CAPRY, TR = 34–50 ms; TE = 5–9 ms, flip angle = 45–50 degrees, FOV = 24–26 cm, slice thickness = 3.0–3.1 mm, number of slices = 60 contiguous, matrix = 256 × 256, number of excitations = 1. On Siemens systems, the following parameters were used for the volumetric acquisition: pulse sequence = 3D-FLASH, TR = 40 ms, TE = 10 ms, flip angle = 40 degrees, FOV = 30 cm, slice thickness = 3.1 mm, number of slices = 60 contiguous, matrix = 256 × 256, number of excitations = 1. Imaging parameters were selected based on the pulse sequence that established a comparable gray-white contrast-to-noise across all image acquisitions (Filipek, Kennedy, Rademacher & Caviness, 1990; Filipek, Richelme, Kennedy & Caviness, 1994). Images on the two systems were found to be comparable for quantitative segmentation analysis (Filipek, Kennedy, Pitcher & Caviness, 1991). To ensure that the use of multiple imaging systems was not a confounding factor in this study, scanner type was included as a covariate in all statistical analyses.

### Image analysis

#### Image positional normalization

Imaging data was analyzed on Sun Microsystems, Inc. (Mountainview, CA) workstations. The initial image data set was normalized with respect to Talairach stereotactic space, wherein the anterior–posterior commissure line specifies the X-axis, a vertical rising from the X-axis through the interhemispheric fissure represents the Y-axis, and a transverse orthogonal line with respect to X and Y coordinates represents the Z-axis (Talairach & Tournoux, 1988). Coronal, axial and sagittal planes used in the morphometric algorithms were then derived computationally (Kennedy, Meyer, Filipek & Caviness, 1994), minimizing the need for precise uniformity of head position at the time of imaging.

Neuroanatomic segmentation was performed using semi-automated algorithms based upon intensity contour mapping and differential intensity contour algorithms that have been previously described (Filipek, Kennedy, Caviness, Spraggins, Rossnick & Starewicz, 1989; Filipek

**Table 3** Descriptive statistics for unadjusted volumes. Volumes are expressed in cubic centimeters. The overall *F* test of group differences was obtained using a multivariate general linear model for correlated data, controlling for age, sex and scanner:  $F(8, 53) = 3.07$ ,  $p = 0.006$ . Significance levels in table refer to univariate tests of total brain and regional volume differences. Effect size (*ES*) = (DLD mean – Control mean) / pooled standard deviation

	DLD group		Control group		DLD × control	
	Mean (cc)	SD	Mean (cc)	SD	ES	Sig.
<i>Brain Region</i>						
Total Brain Volume	1357.60	178.0	1308.50	110.5	0.34	0.025
Cerebral White Matter	413.80	71.6	370.29	46.9	0.70	0.005
Diencephalon	21.76	3.2	20.58	1.6	0.47	0.10
Globus Pallidus-Putamen	15.12	2.3	14.64	1.2	0.27	0.80
Brainstem	20.85	3.2	20.65	2.1	0.08	0.56
Cerebellum	141.48	17.0	140.48	10.7	0.07	0.63
Cerebral Cortex	705.00	101.8	703.31	77.7	0.02	0.75
Hippocampus-Amygdala	14.11	2.3	14.25	1.6	-0.08	0.92
Caudate	9.46	1.9	10.04	1.2	-0.37	0.29

*et al.*, 1994; Kennedy *et al.*, 1994). Segmentation was performed on coronal images, and divided the brain into gray matter and white matter subdivisions. Cerebral cortex–white matter distinctions were accomplished in a semi-automated fashion, while deep grey nuclei were delineated manually.

The total brain was partitioned into its principal subdivisions: cerebrum (total cerebral volume, excluding ventricles), brainstem, cerebellum and ventricular system. The cerebrum was further segmented into its principal gray matter structures and total cerebral white matter (Table 3) (Filipek *et al.*, 1994). Segmentation of gray from white matter in cerebellum or brainstem could not be performed reliably in this data set. The total number of voxels in each brain structure determined its volume.

#### Data analysis

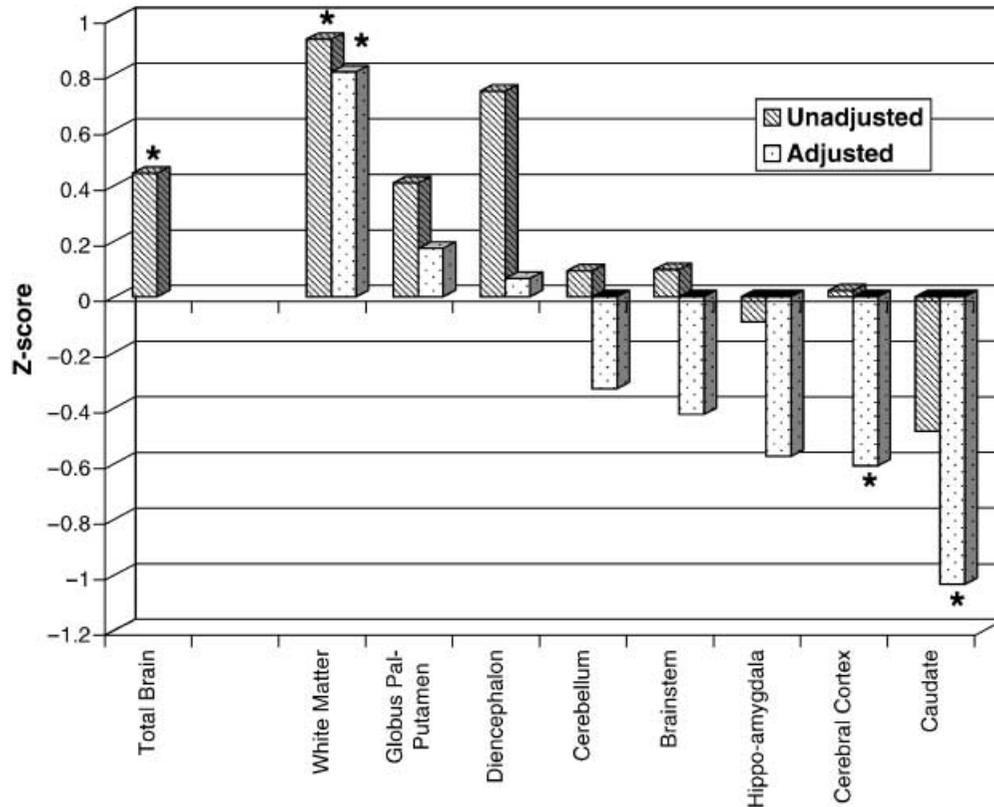
Statistical computations were performed using SPSS (SPSS Inc., Chicago, IL) and SAS (SAS Institute Inc., Cary, NC) statistical analysis software. Graphics were generated by Excel (Microsoft, Redmond, WA). A univariate general linear model (GLM) was used to test for differences in total brain volume between DLD and control children, controlling for age and scanner type and including a sex by diagnosis interaction term. Multivariate general linear models for correlated data (GLM-CD) (Cnaan, Laird & Slasor, 1997), which rely on maximum likelihood estimation, were used to test the composite, or omnibus, null hypothesis of no difference overall (i.e. when considering all brain subdivisions simultaneously) between DLD and control subjects. This model was appropriate given that the data were found to be approximately normally distributed and that there were, as expected from neuroanatomical constraints, high correlations between some brain regions.

The GLM-CD allows for the presence of significant correlations in dependent variables and accounts for any error this might yield in the calculation of standard errors associated with parameter estimates.

A primary multivariate GLM-CD was run on all regional brain volumes to test for diagnosis and sex by diagnosis effects, while controlling for possible effects of age and scanner. Volumes for the following subdivisions were included as dependent variables: brainstem, cerebellum, cerebral cortex, cerebral white matter, hippocampus-amygdala, caudate, globus pallidus-putamen and diencephalon. To avoid statistical complications associated with part–whole comparisons (Darlington, 1990), total brain volume was analyzed separately, since each region is a subset of the total brain. If a significant overall difference between groups was discerned, univariate comparisons between groups were performed for each region using a standard GLM, while controlling for any effects of age, sex and scanner.

In order to determine whether any unadjusted volume differences between the DLD and control children were simply due to differences in overall brain size (Mathalon, Sullivan, Rawles & Pfefferbaum, 1993), we also looked at proportional volumes. This involved testing for differences in brain volumes while statistically adjusting for group differences in overall brain volume, by performing an additional GLM-CD that included total brain volume, as well as age, scanner and sex, as covariates. Again, univariate tests were then computed to localize any differences between DLD and control children. Finally, a third GLM-CD was run on only gray matter cerebral regions while controlling for total gray matter volume (i.e. white matter volume excluded); age, sex and scanner were also included as covariates.

Effect sizes (Cohen, 1988) of the differences between groups were estimated for each region as follows: mean



**Figure 1** DLD unadjusted and adjusted Z-scores standardized to controls. Z-scores were calculated for each subject standardized to the control mean and standard deviation. Mean unadjusted volume Z-scores are indicated by speckled bars; mean adjusted volume Z-scores are indicated by hatched bars. Significant ( $p < .05$ ) pairwise comparisons are indicated by asterisk above or below the bar.

DLD volume minus mean control volume divided by the pooled standard deviation of DLD and control volumes. To calculate effect sizes for adjusted volumes, volumes for each brain were divided by total brain volume and converted to a percentage. Means and pooled standard deviations for these percentages were then used in the effect size calculation, while all statistical tests were performed by controlling for total brain volume using a regression-based approach. Effect size estimates provide useful universal measures of the magnitude of differences between groups, since they are unaffected by sample size and are comparable across studies.

## Results (Figures 1–2; Tables 3 & 4)

### Unadjusted volumes (Figures 1 & 2, Table 3)

Total brain volume was greater in DLD children (1357.6 cc) when compared to controls (1308.5 cc) [ $F(1, 48) = 5.4, p = .025$ ]. Furthermore, the sex by diagnosis interaction was not significant ( $p = .44$ ), even though a signi-

ficant main effect of sex was found, with males showing significantly larger total brain volumes as compared with females [ $F(1, 48) = 5.1, p = .029$ ]. A GLM-CD revealed a significant difference in unadjusted mean brain volumes between DLD and control children while controlling for effects of age, sex and scanner [ $F(8, 53) = 3.07, p = .006$ ]. Post-hoc pairwise univariate tests revealed a single significant regional difference between DLD and control children: cerebral white matter volume [ $F(1, 53) = 8.47, p = .005$ ] was 13% larger in the DLD sample (413 cc for DLD and 370 cc in the control sample). This difference was uniform bilaterally, with DLD brains showing significantly increased white matter volume in both right and left hemispheres ( $p = .01$  and  $p = .03$ , respectively). Furthermore, white matter volume was 18% greater among DLD females as compared with control females (423 cc vs. 326 cc, respectively), and only 8% greater in DLD than controls among the males (416 cc vs. 384 cc, respectively). However, the sex by diagnosis interaction was not significant when considering all structures simultaneously [ $F(8, 53) = .94, p = .504$ ] or for pairwise between-group comparison for any individual brain structures.

**Table 4** Descriptive statistics for adjusted volumes. Regional brain volumes are presented as percentages of total brain volume. Overall F test of group differences was obtained using a multivariate general linear model for correlated data, controlling for total brain volume, age, sex and scanner:  $F(8, 53) = 2.92$ ,  $p = 0.009$ . Effect size (ES) = (adjusted DLD mean – adjusted Control mean) / pooled standard deviation of adjusted volumes. Significance levels in table were derived from univariate general linear models, covarying for total brain volume, age, sex and scanner

	DLD group		Control group		DLD × control	
	Mean (cc)	SD	Mean (cc)	SD	ES	Sig.
<i>Brain Region</i>						
Central White Matter	30.39	2.9	28.29	2.6	0.73	0.01
Caudate	0.70	0.1	0.77	0.1	–0.70	0.02
Cerebral Cortex	51.93	2.9	53.70	2.9	–0.59	0.03
Globus Pallidus-Putamen	1.12	0.1	1.12	0.1	–0.06	0.35
Hippocampus-Amygdala	1.04	0.1	1.09	0.1	–0.43	0.38
Diencephalon	1.61	0.2	1.58	0.1	0.21	0.39
Brainstem	1.54	0.1	1.58	0.2	–0.34	0.57
Cerebellum	10.49	1.0	10.78	0.9	–0.30	0.64

#### *Volumes of segmented structures adjusted for total brain volume (Figures 1 & 2, Table 4)*

A GLM-CD showed that DLD and control subjects differed significantly in terms of brain volumes of segmented structures, adjusted for total brain volume, and while also controlling for age, sex and scanner [ $F(8, 53) = 2.9$ ,  $p = .009$ ]. Post-hoc univariate analyses showed adjusted cerebral white matter volume was 7% larger in DLD [ $F(1, 53) = 7.0$ ,  $p = .011$ ], and white matter displayed the highest effect size (0.73) of all the adjusted volumes. However, several adjusted volumes of gray matter subdivisions were smaller in DLD: cerebral cortex was 3.5% smaller [ $F(1, 53) = 5.0$ ,  $p = .03$ ] and caudate was 11% smaller [ $F(1, 53) = 5.3$ ,  $p = .026$ ]. Furthermore, when the right and left hemispheres of DLD and control brains were compared separately, cerebral cortex and caudate were relatively smaller in both hemispheres (for cerebral cortex, RH:  $p = .03$ ; LH:  $p = .01$ ; for caudate, RH:  $p = .04$ ; LH:  $p = 0.01$ ) and cerebral white matter was relatively larger in both hemispheres (RH:  $p = .02$ ; LH:  $.01$ ).

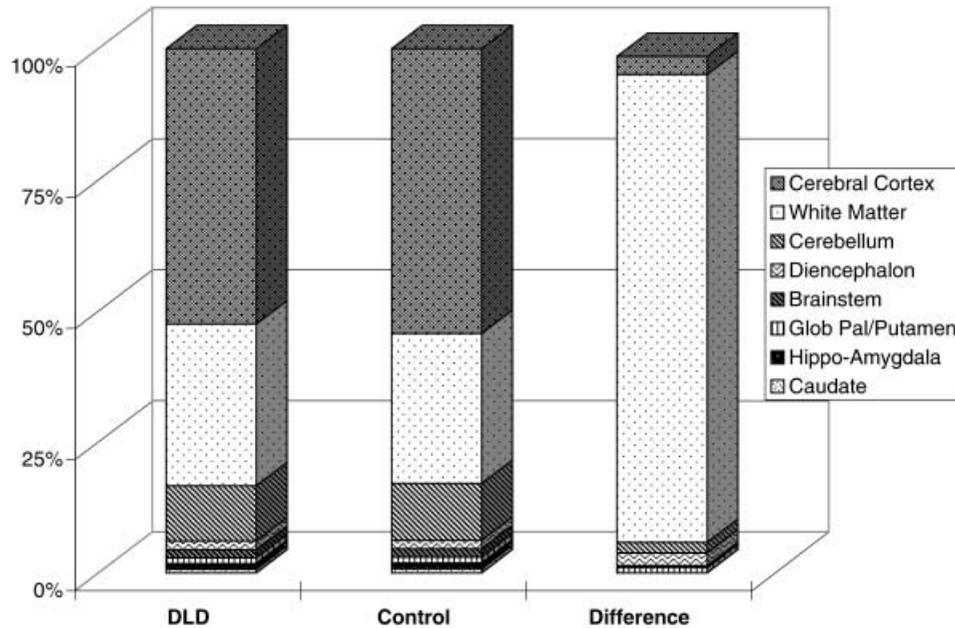
#### *Cortical gray matter regions adjusted for total cerebral gray matter volume*

Gray matter volumes, adjusted for total cerebral volume excluding white matter, were analyzed with a GLM-CD with age, sex and scanner as covariates. A significant main effect of diagnosis was not found [ $F(5, 53) = 1.78$ ,  $p = .13$ ]. Furthermore, univariate post-hoc comparisons confirmed a lack of any significant differences in gray matter structure volumes between DLD and control children.

## Discussion

The present study is, to our knowledge, the first report of a full morphometric profile of all the major subdivisions of the brain and the principal gray and white matter cortical and nuclear structures of the forebrain of DLD children. The most striking features of this profile are the increased total brain volumes and the altered volumetric relationships between cerebral white matter and cerebral cortical gray matter in the DLD brains. While these DLD brains are modestly larger than controls, the only structure to show significant unadjusted volumetric increase is cerebral white matter. When volumes are adjusted for total brain size, cerebral white matter is still disproportionately larger, but now two gray matter structures, caudate and cerebral cortex, are disproportionately smaller than controls; these latter differences disappear, though, when gray matter adjusted volumes are compared with white matter excluded, suggesting that they are not as robust as the white matter increase. The increase in both unadjusted and adjusted white matter volume thus means that the 3.7% increase in overall brain volume is almost entirely due to the 11.7% volume increase in cerebral white matter (Figure 2). Indeed, white matter accounts for 88% of the total brain volume increase in DLD over controls. While there are intriguing sex differences, with white matter being much larger in females than males relative to controls, a larger sample would be needed to explore these differences.

We are unaware of any prior quantitations of overall white matter volume in DLD in the literature. However, our findings do not constitute the first reported neuro-anatomic abnormality related to white matter in subjects



**Figure 2** Proportions and differences. The left two bars indicate the proportion of total brain volume occupied by each structure in DLD and in Control brains. The right bar divides the total volume difference between DLD and Control brains into the proportion of volume increase in DLD contributed by each brain structure.

with language disabilities. A diffusion tensor imaging study of white matter in dyslexic subjects (Klingberg, Hedehus, Temple, Salz, Gabrieli, Moseley & Poldrack, 2000) revealed differences in anisotropy bilaterally in the white matter of the temporo-parietal region. The anisotropy changes in the left hemisphere were furthermore correlated with reading scores for both control subjects and poor readers. That study sought but did not find differences between groups in either T1-weighted images or between-voxel coherence. Thus the abnormalities reported were not volumetric or related to axonal directionality, but rather were confined to microstructural tissue properties as reflected in fractional anisotropy of diffusion tensors. In our present study we did, however, discern white matter volume differences in T1-weighted images, but we had younger subjects with language rather than reading impairment.

While the finding of increased cerebral white matter is substantial and robust, the significance it may have in relation to the functional disability and its pathophysiological basis is not obvious. With respect to functional disability, the finding of a pervasive anatomic abnormality seems paradoxical in its association with a clinical disorder that manifests predominantly as a specific disability of language. Even if the existence of subtle non-linguistic deficits in subjects with DLD is acknowledged, the disparity in severity between language deficits and deficits in cognitive, memory, motor and special sensory

functions is great enough that the conundrum is not resolved. And with respect to pathophysiology, an argument that the enlarged cerebral white matter in some way is causal to the systems dysfunction would require a model that makes language mechanisms preferentially vulnerable to generalized systems dysfunction. Alteration in white matter may potentially affect or relate to the specificity of brain connectivity, the density of neurons and axons, the ratio of convergent and divergent connections in neural circuits, and axonal conduction properties. To link volumetric enlargement of cerebral white matter to systems dysfunction would require a determination of which of these parameters is affected by this volume increase, and in what ways. The volumetric data we present here can raise these questions but cannot answer them.

Nevertheless, several contemporary debates in the DLD literature appear relevant to evaluating the implications of the pervasively enlarged white matter we report here. These debates counterpose specificity to pervasiveness in various dimensions, regarding (1) the character of underlying abnormalities, (2) the range of deficits and (3) the boundaries and specificity of the disorder.

1. With regard to underlying abnormalities, while some argue that DLD arises from abnormalities in specifically language-related modules (Gopnik & Crago, 1991;

- Hurst, Baraitser, Auger, Graham & Norell, 1990; van der Lely, Rosen & McClelland, 1998; Vargha-Khadem, Watkins, Alcock, Fletcher & Passingham, 1995), others marshal evidence supporting an underlying more basic deficit in either general processing (Kail, 1994; Johnston, Smith & Box, 1997; Montgomery, 2000), or in a specific processing mechanism (Tallal & Stark, 1981; Gathercole & Baddeley, 1995). The white matter enlargement we report is not a modular abnormality, and if it proves to be related to the functional language disorder, it will probably be through a mechanism of generalized processing impairment. Models of how a generalized systems disturbance may lead to the emergence of an uneven profile of functional impairment, and even to a profile suggestive of focality, can be found in connectionist theory, although without linkage to specific tissue abnormalities (Plunkett *et al.*, 1997). The learning capacity of such modeled neural networks can be degraded either through lesioning nodes or through adding noise to connections (which white matter enlargement may do), with certain functions having greater vulnerability to generalized disturbances (Elman, Bates, Johnson, Karmiloff-Smith, Parisi & Plunkett, 1996).
2. With regard to the range of deficits, observations that impairments in DLD are not entirely specific to language are consistent with notions of generalized systems impairment: even if there is selective vulnerability of some functions (such as language), it is unlikely that the problems will be entirely confined to either language or sensory domains. Indeed, there are many reports of multiple more subtle non-linguistic abnormalities in DLD children, including deficits in cognitive tasks (Johnston, 1994; Johnston & Weismer, 1983; Kamhi, Catts, Mauer, Apel & Gentry, 1988; Kamhi, Gentry, Mauer & Gholson, 1990; Rescorla & Goossens, 1992) and processing of social and emotional stimuli (Shields, Varley, Broks & Simpson, 1996a; Farmer, 2000), crossed localization (implying impaired callosal information transfer) (Fabbro, Libera & Tavano, 2002), and motor and neurological abnormalities (Hill, 2001; Noterdaeme, Mildnerberger, Minow & Amorosa, 2002; Owen & McKinlay, 1997; Trauner, Wulfeck, Tallal & Hesselink, 2000), including slow performance of fine motor tasks, balance and limb praxis (Bradford & Dodd, 1994; Powell & Bishop, 1992). These subjects also manifest various functional difficulties as greater demands are placed on the nervous system (Gillam, Hoffman, Marler & Wynn-Dancy, 2002), which would also be expected with a generalized systems impairment, and would lead to a profile showing greater weakness in tasks (including those in linguistic domains) requiring more associational, cross-modal or integrative activity (Boucher, Lewis & Collis, 2000; Mesulam, 1999; Weismer & Evans, 2002). It is possible that a pervasive white matter abnormality could underlie this range of deficits.
  3. With regard to the specificity of underlying pathology, increased white matter has also been discerned in several cohorts of non-retarded autistic subjects (Cody, Keyes-Elstein & Piven, 2001; Courchesne, Karns, Davis, Ziccardi, Carper, Tigue, Chisum, Moses, Pierce, Lord, Lincoln, Pizzo, Schreibman, Haas, Akshoomoff & Courchesne, 2001; Herbert, Ziegler, Deutsch, O'Brien, Lange, Bakardjiev, Hodgson, Adrien, Steele, Makrisk, Kennedy, Harris & Caviness, 2003) whose brains were also somewhat larger than controls. Autism involves language deficits, but also social, emotional and behavioral deficits that are not subtle and are not found in children with DLD. Nevertheless, similarities have been found between some DLD and autistic subjects in relation to the profile of language deficits (Kjelgaard & Tager-Flusberg, 2001; Rapin, 1996). A recent MRI-based volumetric comparison of the brains of children with DLD to those of children with autism (which included the current subjects but also another DLD sample) found similar alterations in linear scaling between diencephalon, cerebral white matter and cerebral cortex volumes in the two groups as compared to controls (Ziegler, Herbert, Hodge, Deutsch, Steele, McGrath, Makris, Kennedy, Harris, Tager-Flusberg & Caviness, 2002). On the one hand, these shared anatomical abnormalities in members of two diagnostic groups who may both have language deficits but who differ in other functional and anatomical respects (Courchesne, Lincoln, Yeung-Courchesne, Elmasian & Grillon, 1989; Howlin, Mawhood & Rutter, 2000; Mawhood, Howlin & Rutter, 2000; Rapin, 1998; Shields *et al.*, 1996a; Shields, Varley, Broks & Simpson, 1996b) raises the possibility that the cerebral white matter enlargement is not a primary problem, but instead in some way a secondary consequence of an as yet undefined systems or processing abnormality, and itself does not contribute to language dysfunction in DLD. Indeed, white matter enlargement might have no functional effect in itself. On the other hand, the overlap may imply some continuity between DLD and autism, consistent with suggestions that developmental cognitive disorders are on a continuous spectrum rather than being a series of discrete subtypes (Karmiloff-Smith, 1998; Paterson *et al.*, 1999) and that notions of discrete subtypes may need to give way to a medical model articulating multiple risk and protective factors (Bishop, 2001). In either case, given the overlapping neuroanatomical phenotype, DLD and

autistic subjects with and without this white matter enlargement should be compared regarding language phenotype, and similarities and differences between the two groups should be further characterized on a more fine-grained neuroanatomical level.

This study is limited to volumetric data obtained from one small cross-sectional sample, and furthermore reports only the first of a series of analytical stages. Future papers utilizing the methods of parcellation of these brains into subunits of cerebral cortex (Rademacher, Galaburda, Kennedy, Filipek & Caviness, 1992) and subunits of subcortical gray and white matter (Meyer, Makris, Bates, Caviness & Kennedy, 1999; Makris, Meyer, Bates, Kennedy & Caviness, 1999; Rademacher *et al.*, 1992) will report morphometric findings at finer levels of resolution. Regarding the mild relative decrease in caudate volume we report, it will require future studies to discern whether this is a subtle difference pervading subjects with the disorder or whether it may be a more robust difference in a subset who may also have related functional deficits, such as expressive or articulatory difficulties or apraxia. And while the volumetric differences in this study between DLD and controls regarding cerebral cortex were less pronounced than those regarding white matter, the cortical parcellation data to be explored in future studies can discern regional volume differences in cerebral cortex that are washed out in the measure here used which is of total cortical volume (Herbert *et al.*, 2001). It should be remembered, though, that while more fine-grained anatomic analysis of cortex and white matter may identify more specifically regional disparities, such findings still would not resolve the paradox posed by the disparity between the generalized white matter enlargement we report here and the predominance of language among the deficits in subjects with DLD. For further characterization of the nature of the white matter abnormality, fresh data will be required that will allow comparisons of volumetric with other neuroimaging characterizations of white matter, such as magnetization transfer and diffusion tensor imaging. The findings from these studies may in turn suggest other neurobiological investigations to characterize the contributions of neuronal, axonal, myelin and neuropil compartments to the macroscopic volumetric changes. Larger imaging samples may also allow us to explore the intriguing male–female differences in white matter enlargement that did not achieve significance in this study, as well as to gain more information about the apparent relative volume reductions in cerebral cortex and caudate in DLD.

The documentation of a widespread abnormality in white matter in DLD brains opens a new domain for

consideration, and offers a possible neuroanatomical basis for the diversity of phenotypic features associated with language impairment in this disorder, as well as a possible neuroanatomical correlate for the generalized processing impairment that may underlie the disorder. The quantification of a volumetric abnormality in white matter thus opens multiple new possibilities for understanding the neurobiology underlying DLD.

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