

Brain asymmetries in autism and developmental language disorder: a nested whole-brain analysis

M. R. Herbert,^{1,2,7} D. A. Ziegler,^{1,2,9} C. K. Deutsch,^{4,6,8} L. M. O'Brien,¹⁰ D. N. Kennedy,^{1,2,3} P. A. Filipek,¹¹ A. I. Bakardjiev,¹² J. Hodgson,¹³ M. Takeoka,⁵ N. Makris^{1,2} and V. S. Caviness Jr^{1,2}

¹Center for Morphometric Analysis and Departments of ²Neurology and ³Radiology, Massachusetts General Hospital, Harvard Medical School, ⁴Department of Psychiatry, Harvard Medical School, ⁵Children's Hospital, Boston, ⁶Psychobiology and Medical Genetics Programs, Eunice Kennedy Shriver Center, Waltham, Department of ⁷Neurology, ⁸Mailman Research Center, McLean Hospital, Belmont and ⁹Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, MA, ¹⁰Department of Mathematics, Colby College, Waterville, ME, ¹¹Department of Pediatrics, University of California, Irvine, ¹²Department of Infectious Diseases, Children's Hospital Oakland, CA and ¹³Tennessee Center for the Study and Treatment of Dyslexia, Middle Tennessee State University, Murfreesboro, TN, USA.

Correspondence to: Martha R. Herbert, MD, PhD, Pediatric Neurology/Center for Morphometric Analysis, Massachusetts General Hospital, Harvard Medical School, 149 13th Street, Room 6012, Charlestown, MA 02129 USA. E-mail: mherbert1@partners.org

Summary

We report a whole-brain MRI morphometric survey of asymmetry in children with high-functioning autism and with developmental language disorder (DLD). Subjects included 46 boys of normal intelligence aged 5.7–11.3 years (16 autistic, 15 DLD, 15 controls). Imaging analysis included grey–white segmentation and cortical parcellation. Asymmetry was assessed at a series of nested levels. We found that asymmetries were masked with larger units of analysis but progressively more apparent with smaller units, and that within the cerebral cortex the differences were greatest in higher-order association cortex. The larger units of analysis, including the cerebral hemispheres, the major grey and white matter structures and the cortical lobes, showed no asymmetries in autism or DLD and few asymmetries in controls. However, at the level of cortical parcellation units, autism and DLD showed more asymmetry than controls. They had a greater aggregate volume of significantly asymmetrical cortical parcellation units (leftward plus rightward), as well as a substantially larger aggregate volume of right-asymmetrical cortex in DLD and autism than in controls; this rightward bias was more pronounced in autism than

in DLD. DLD, but not autism, showed a small but significant loss of leftward asymmetry compared with controls. Right : left ratios were reversed, autism and DLD having twice as much right- as left-asymmetrical cortex, while the reverse was found in the control sample. Asymmetry differences between groups were most significant in the higher-order association areas. Autism and DLD were much more similar to each other in patterns of asymmetry throughout the cerebral cortex than either was to controls; this similarity suggests systematic and related alterations rather than random neural systems alterations. We review these findings in relation to previously reported volumetric features in these two samples of brains, including increased total brain and white matter volumes and lack of increase in the size of the corpus callosum. Larger brain volume has previously been associated with increased lateralization. The sizeable right-asymmetry increase reported here may be a consequence of early abnormal brain growth trajectories in these disorders, while higher-order association areas may be most vulnerable to connectivity abnormalities associated with white matter increases.

Keywords: association cortex; connectivity; lateralization; neural systems development; specific language impairment

Abbreviations: DLD = developmental language disorder; IQ = intelligence quotient; PU = parcellation unit; SI = symmetry index

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Introduction

Autism and developmental language disorder (DLD) are both behaviourally defined disorders that emerge in early childhood. Both involve language impairment, and autism additionally involves impaired social reciprocity as well as repetitive or restricted behaviours (American Psychiatric Association, 1994; Rapin and Dunn, 2003; Rapin *et al.*, 2003). In autism there is increasing evidence that the disorder is associated with a tendency towards large brain volume in childhood (Bailey *et al.*, 1998; Fombonne, 2000; Aylward *et al.*, 2002), driven predominantly by increased white matter (Courchesne *et al.*, 2003; Herbert *et al.*, 2003a). In DLD, brain investigations have largely focused on language regions of the brain, although the few published whole-brain morphometric studies include some reports of increased brain volume in this disorder as well (Filipek *et al.*, 1992; Woodhouse *et al.*, 1996; Herbert *et al.*, 2003b).

Work in our laboratory on a series of brains of children with autism and DLD has identified multiple similarities between these two groups, though with modest differences in degree: both share a pervasive morphometric anomaly—notably, larger than normal brain and white matter volumes—but it is more pronounced in autism (Herbert *et al.*, 2003a, b). The white matter enlargement is non-uniformly distributed, involving subcortical radiate white matter but sparing the corpus callosum (Herbert *et al.*, 2004). Thus, the volume comprising intrahemispheric connections is disproportionately enlarged compared with interhemispheric white matter, and this may have an impact on brain asymmetry. In this study we will focus on anatomical asymmetries, which can be manifestations of regional specialization of systems organization where there are functional differences between the left and right hemispheres. Anomalous patterns of asymmetries may indicate altered regional specialization as well as impaired information processing (Hynd *et al.*, 1995). We previously reported asymmetry reversal in language-associated cortex in autism (Herbert *et al.*, 2002) that has recently been replicated (De Fosse *et al.*, 2004). Here, we extend our working hypothesis to predict that systems organization is disrupted in autism and DLD, and that this disruption will be reflected more broadly in anomalous patterns of cerebral volume asymmetry, with distinctive patterns expected in these substantially different clinical conditions.

Our data are drawn from a comprehensive segmentation of the entire brain and a parcellation of the cerebral cortex, allowing analyses at multiple nested anatomical levels. First, we examined large-scale patterns of asymmetry in the hemispheres, in the principal grey and white matter structures of the brain, in the cerebral lobular partitions and in aggregated cortical parcellation units (PUs). Secondly, because we parcellated the entire cortex, we were able to explore asymmetries in groupings of PUs approximating the primary sensorimotor cortex, unimodal association cortex and higher-order association cortex. It has been proposed that more complex processing is impaired in autism (Minshew *et al.*, 1997), and that rapid

processing is impaired in DLD (Benasich and Tallal, 2002). Association cortex may provide an anatomical correlate for complex or rapid processing impairments in these disorders. Our hypothesis is that because cortical components of neural systems with greater interconnectivity are likely to be preferentially affected by abnormalities of white matter, we should therefore see greater differences from controls in volume asymmetry in higher-order association cortex. In addition, because language impairments are found in both autism and DLD, we also looked for differences among groups in a subset of association cortex PUs that are considered to be involved in language functions. Since these brains are the products of atypical development, it may be that functional divisions will differ from controls in unknown ways, or that anatomical underpinnings of abnormalities in complex processing (including language) may involve widely distributed circuit-disrupting abnormalities. We therefore performed a comparison of asymmetry patterns across the entire cerebral cortex, and hypothesized that these three groups would differ from each other at this level. This study is thus the first comprehensive whole-brain survey of volume asymmetry in high-functioning autism and DLD.

Methods

Subjects

Quantitative volumetric analysis was performed on brain MRIs of 46 boys (16 autistic, 15 DLD, 15 normal control) between 5.7 and 11.3 years of age (Caviness *et al.*, 1996b). Subjects were matched by group on handedness: 38 boys were right-handed (13 autistic, 12 DLD, 13 control) and eight boys were left-handed (three autistic, three DLD, two controls). All subjects with autism or DLD had performance intelligence quotients (IQs) greater than 80. IQ did not differ significantly between these groups ($P = 0.77$); the mean performance IQ for autism was 110 (± 18); for DLD it was 108 (± 24). Autistic and DLD children were recruited between 1985 and 1988 by clinical referral or by participation in school special needs programmes (Rapin, 1996). The control subjects were recruited specifically to the imaging arm of the study; eligibility required normal developmental history without seizures or significant head injury, normal school performance, and normal neurological examination, although IQ was not measured for controls (Caviness *et al.*, 1996b). 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. All of the scans analysed in this study were judged by a clinical neuro-radiologist to be normal. No sedation was used for scanning. All participating institutions granted Human Subjects Committee approval, and the parents of all the study children gave written informed consent.

Diagnostic classification

The autistic and DLD subjects were recruited in the late 1980s before they entered school as part of a larger study of children

with disorders of communication. Recruitment was conducted for subjects with autism and with developmental language disorder (as well as mental retardation, although such subjects are not included in the current study) (Rapin, 1996). Diagnostic instruments meeting standards at the time the study was conducted were used for classification, and expert clinicians confirmed all diagnoses. While children with DLD were referred for language disorders and not for autism, all children regardless of their diagnoses were screened using the three-part Wing Autistic Disorder Interview Checklist (WADIC) (Rapin, 1996), a parent questionnaire covering the three core domains of impairment in autism. Children meeting criteria for autism were then confirmed or disconfirmed in their diagnoses by a blinded child psychiatrist who performed a structured comprehensive evaluation with determination of diagnosis according to DSM III-R criteria that were current at the time of data acquisition. In the overall sample, among the non-autistic subjects (i.e. 311 children who were either DLD or a non-autistic low-IQ group not included in the current report), 91% of children (i.e. 283) had no suspicion of autism by the WADIC and autism was excluded in the remaining 9% by psychiatric interview (Rapin, 1996).

The DLD classification itself was made in the presence of a non-verbal IQ above 80 plus significant relative deficiency in language measures, meaning either (i) a score on the Test of Early Language Development (Hresko *et al.*, 1981) that was 1 SD below the mean NVIQ score, or (ii) a mean length of utterance score that was 1 SD below the mean for the child's chronological age.

Image acquisition

MRI was performed on either General Electric 1.5 T Signa (Milwaukee, WI, USA) or Siemens 1.5 T Magnetom (Iselin, NJ, USA) systems. Scanning was performed between 1989 and 1992. On the GE system, 13 autistic, seven DLD and 14 control subjects were scanned. Volumetric acquisition parameters were: pulse sequence = 3D-SPGR or 3D-CAPRY, repetition time (TR) = 34–50 ms; echo time (TE) = 5–9 ms, flip angle = 45–50°, field of view (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, three autistic subjects, eight DLD subjects and one control subject were scanned. Volumetric acquisition parameters were: pulse sequence = 3D-FLASH, TR = 40 ms, TE = 10 ms, flip angle = 40°, FOV = 30 cm, slice thickness = 3.1 mm, number of slices = 60 contiguous, matrix = 256 × 256, number of

excitations = 1. Images on the two systems were found to be comparable for quantitative segmentation analysis (Filipek *et al.*, 1991). In addition, 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 statistical analyses whenever possible; a significant effect of scanner was not found in any of these analyses.

Image positional normalization

Imaging data were analysed on Sun Microsystems (Mountain View, CA, USA) 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 the *x* and *y* coordinates represents the *z* axis (Talairach and Tournoux, 1988). Coronal, axial and sagittal planes used in the morphometric algorithms were then derived computationally (Kennedy *et al.*, 1994), minimizing the need for precise uniformity of head position at the time of imaging.

Image analysis

For both segmentation and parcellation, image analysis was performed on randomly assigned sets of brains by operators blinded to diagnosis. Neuroanatomical segmentation was performed using semi-automated algorithms based upon intensity contour mapping and differential intensity contour algorithms that have been described previously (Fig. 1A and B) (Filipek *et al.*, 1989; Filipek *et al.*, 1994; Kennedy *et al.*, 1994). Segmentation was performed on coronal images, dividing the brain into grey matter and white matter subdivisions, and required approximately 1 week per brain. Cerebral cortex–white matter distinctions were segmented in a semi-automated fashion, while deep grey nuclei were delineated manually. Segmentation was performed between 1990 and 1993 by five raters, who met laboratory standards of reliability (Filipek *et al.*, 1994; Seidman *et al.*, 1999).

The neocortical ribbon was then parcellated into 48 primarily gyral-based PUs per hemisphere (Fig. 1C), according to a procedure described previously (Rademacher *et al.*, 1992; Caviness *et al.*, 1996a; Kennedy *et al.*, 1998). Briefly, sulcal patterns were identified and labelled by a neuroanatomically trained rater, on multiplanar orthogonal views allowing the sulcal markers to be tracked

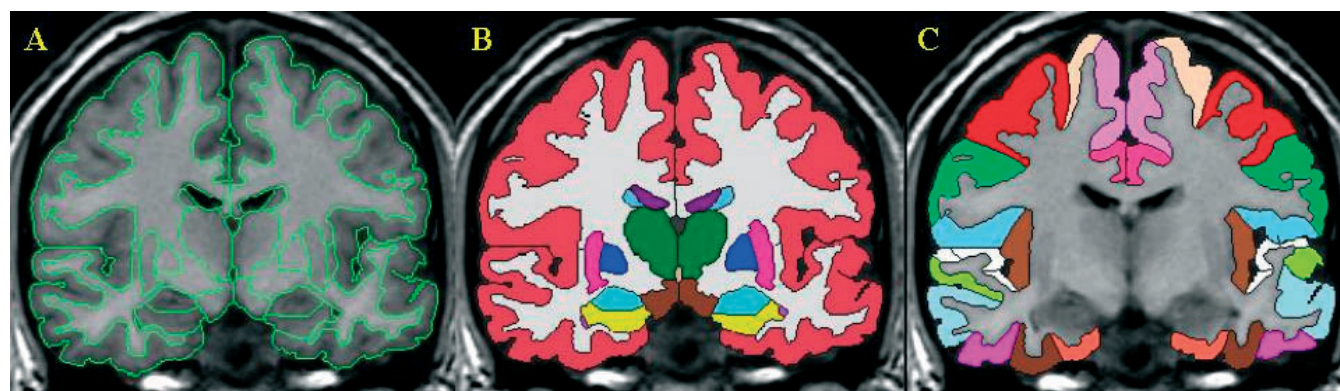


Fig. 1 Grey–white segmentation and cortical parcellation. (A) Segmentation outlines. (B) Labeled brain segmentation structures. (C) Parcellation of the cortical ribbon in a coronal slice.

three-dimensionally. In addition, anatomical markers for other mainly anterior–posterior divisions of larger gyral units were identified. A canonical set of PUs was then identified and labelled with a colour-code system. Cortical parcellation was performed between 1995 and 1998 by four raters who met the previously reported laboratory standards for inter-rater reliability for this method (Caviness *et al.*, 1996a) Volumes were derived by summing the voxels in each cortical PU. Graphical representation maps of the cortical PUs are included in Fig. 2 (the PU legend is in Table 2). Comparisons between volumes of anatomical units on the left and right hemispheres were calculated and expressed as a symmetry index, SI (Galaburda *et al.*, 1987), using the formula $SI = 2(L - R)/(L + R)$ and multiplied by 100 to convert the score to a percentage. Positive values indicate left-sided preponderance.

Data analysis

Analyses of asymmetry were performed for anatomical regions in a nested hierarchy that included (i) total brain volume, (ii) all segmented divisions of total brain volume (cerebral cortex, cerebral

white matter, cerebellum, caudate, globus pallidus–putamen, diencephalon, brainstem), (iii) lobes of the cerebral cortex (derived by grouping cortical PUs according to lobe) and (iv) individual cortical PUs for the entire cerebral cortex. A symmetry index was calculated for anatomical units at each of these levels. To classify each structure as being significantly left- or right-asymmetrical, one-sample Student’s *t* tests were used to assess the probability that the mean SI for each segmented structure or PU was non-zero (i.e. significantly asymmetrical). Since these one-sample tests were used only for general classification, adjustments for multiple comparisons were not performed. For those structures with significant asymmetry, the sign of the asymmetry index determined classification as left-asymmetrical or right-asymmetrical. Structures or PUs for which the one-sample *t*-test was not significant were classified as being symmetrical.

Assessment of between-group asymmetry differences

Multivariate general linear models for correlated data (GLM-CD) (Cnaan *et al.*, 1997) were used to test for differences in asymmetry

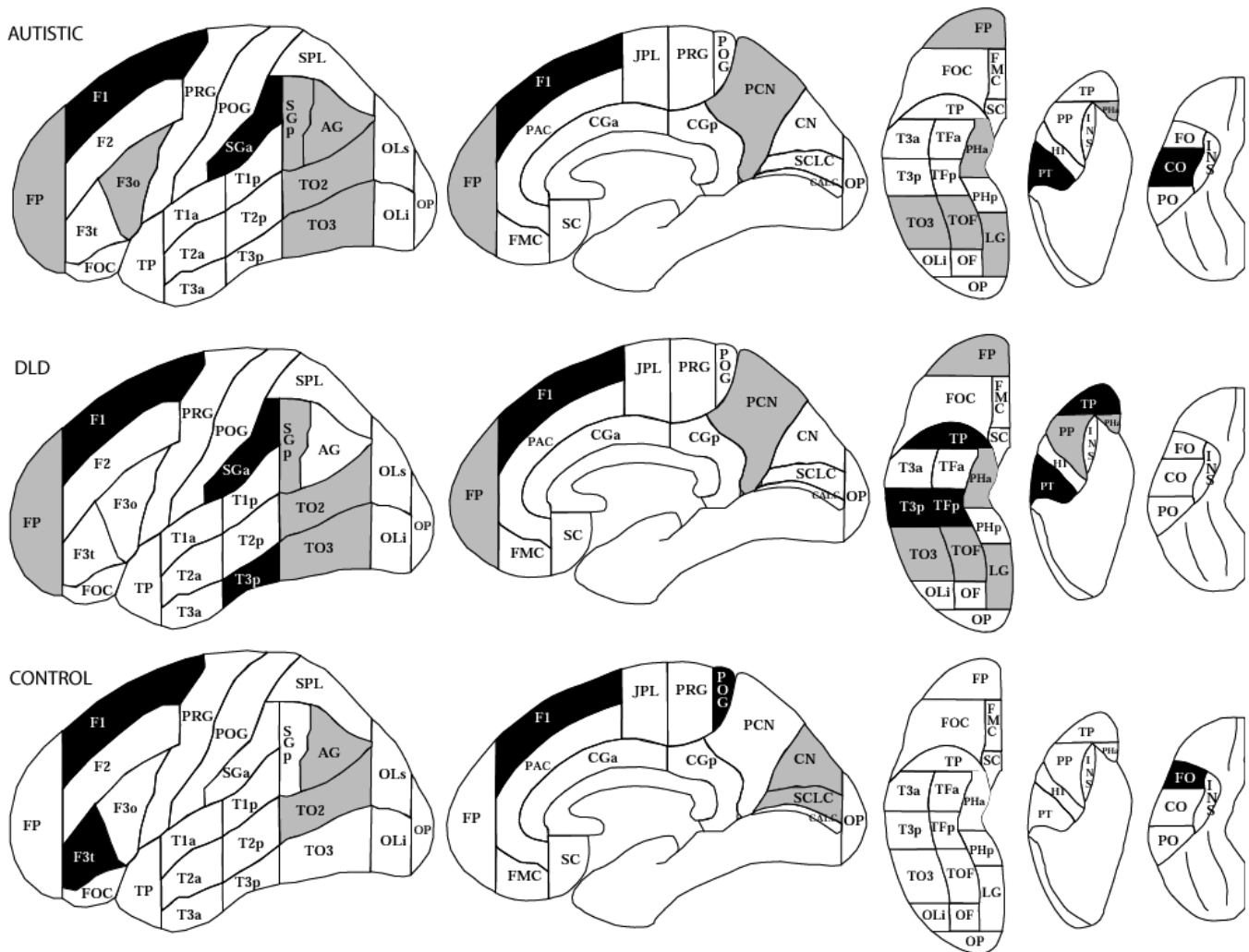


Fig. 2 Asymmetry in each parcellation unit by group. Black indicates units with significant leftward asymmetry, and grey indicates significant rightward asymmetry. Non-shaded units were not significantly asymmetrical in either direction. Parcellation unit abbreviations are presented in Table 2.

between autistic, DLD and control boys in segmented structures, lobes and PUs grouped by processing type. In each model, handedness, scanner and age served as covariates. When a significant multivariate difference was found, the classification method described above was then used at that level of analysis for *post hoc* comparisons. This method was chosen over the more traditional bivariate parametric *post hoc* tests for between-group differences, since it is possible to have a significant difference in mean SI values between two groups without the SI actually being significantly different from zero (i.e. asymmetrical) for one or both groups. Thus, the *post hoc* statistical method we employ here is more conservative.

Aggregate volumes of PU with significant asymmetry

Aggregate volume of asymmetry in either direction was calculated as follows. (i) For each individual subject, we summed bilateral volumes of all PU with significant asymmetry (all shaded units in Fig. 2) within the diagnostic group of that individual. (ii) We then calculated means of these totalled volumes for all subjects in each group, performing the procedure separately for autistic, DLD and control subjects. (iii) Finally we calculated the percentage of cerebral cortex with significant asymmetry for each group by dividing the mean of the aggregate volume by the total mean cortical volume of that group. Aggregate volumes of left-asymmetrical and of right-asymmetrical cortex were calculated by repeating this process, taking into consideration the direction of the asymmetrical PU (leftward or rightward), yielding volumes and percentages of cortex with either leftward or rightward asymmetry for each group of subjects. Right : left volume asymmetry ratios were then calculated for each group using the means of the directional aggregate volumes.

For each of the aggregate volume asymmetry analyses (i.e. significantly left-, right- or left- plus right-asymmetrical cortex), a general linear model (GLM) was used to test for differences between groups, while covarying for handedness, age, scanner and total cerebral cortex volume. Total cerebral cortex volume was included in the model to take account of individual and group differences in total cortical volume.

Comparisons of cortical parcellation units by processing type

To determine whether differences in asymmetry between autistic, DLD and control boys were specific to PU involved in associational processing, the PU were classified according to general functional type. Based on previously published PU classifications (Rademacher *et al.*, 1992), we were able to classify 40 of the PUs as being predominantly (i) primary sensory or motor cortex (six PUs), (ii) unimodal association cortex (17 PUs) or (iii) higher-order association cortex (17 PUs). The remaining eight PUs could not be clearly classified because of overlapping functions within the defined boundaries of the PUs. All PUs and their classifications are listed in Table 2.

Comparison of language-related cortical parcellation units

A subset of PU was identified, based on previous research, as associated with language function (Caplan *et al.*, 1995, 1996). This subset of PUs included the angular gyrus, inferior frontal gyrus (pars opercularis and pars triangularis), frontal operculum,

insula, planum polare, planum temporale, anterior and posterior supramarginal gyri, and anterior and posterior superior temporal gyri. A multivariate GLM-CD, as described above, was used to test for group differences in this set of PUs. In addition, since the classifications of PUs into groups based on processing type and based on involvement in language processing are not mutually exclusive, we wished to assess whether significant multivariate group differences at the level of associational processing might be simply the result of including language-related PUs in the model. To do this, if a significant difference was found for an entire group of PUs, the model was run again after excluding language-related PUs.

Patterns of asymmetry across all units of parcellated cortex

Finally, we performed an additional *post hoc* analysis of asymmetry in all 48 PUs in order to assess the extent of similarity in asymmetry patterns across the entire cerebral cortex among each of the three pairwise group comparisons. Mean SIs were calculated for each of the 48 PUs in each diagnostic group. One-sample Student's *t* tests were used to classify each PU as significantly left-asymmetric, significantly right-asymmetric, or not asymmetric, as described above. A contingency table was derived for three pairwise comparisons (autism \times control, DLD \times control and autism \times DLD). For each comparison, there were two possible outcomes: each PU was classified as 'same' if both the direction and the significance of asymmetry as described above were the same; otherwise it was classified as 'different'. A χ^2 test of independence was then used to test for differences in the number of PUs with same or different asymmetry in each pairwise comparison among the three groups.

Results

Asymmetry in hemispheres and segmented cerebral structures

No significant asymmetry for autistic, DLD or control groups was discerned when considering total hemispheric volume (Table 1, Fig. 3). However, when the hemispheres were segmented, a multivariate GLM-CD revealed a significant difference in asymmetry between autistic, DLD and control boys [$F(14,42) = 2.1, P = 0.036$]. Of the seven segmented structures, in controls two were significantly left-asymmetrical: cerebral cortex (SI 1.6; $P = 0.013$) and two were significantly right-asymmetrical: caudate (SI = 3.547, $P = 0.034$); and cerebral white matter (SI = -3.363, $P = 0.007$) and globus pallidus-putamen (SI = -2.095, $P = 0.039$). By contrast, no segmented structures showed significant asymmetry in either autism or DLD. Anatomical structures and units with significant asymmetry are highlighted in Table 1; left asymmetry has a positive sign and is in bold face, while right asymmetry has a negative sign and is italicized.

Asymmetry in cerebral cortical lobes

A significant multivariate difference in asymmetry of cerebral cortical lobes was not found between autistic, DLD and control boys [$F(8,42) = 1.4, P = 0.24$]. Furthermore, when

Table 1 Segmented structures: asymmetry

Structure	Mean SI with direction		
	Autistic	DLD	Control
Total brain	-0.353	-0.137	0.151
Cerebral cortex	0.386	0.389	1.599*
Frontal lobe	0.008	-0.005	0.025*
Temporal lobe	0.001	0.013	0.008
Parietal lobe	-0.016	-0.030	0.010
Occipital lobe	0.024	0.033	0.024
Cerebral white matter	-1.999	-0.877	-3.363*
Caudate	-0.442	-1.610	3.547*
Cerebellum	0.922	0.620	1.280
Diencephalon	-1.003	0.063	1.896
Globus pallidus-putamen	0.081	0.359	-2.095*
Hippocampus-amygdala	-0.621	2.788	-1.446

Bold numbers (and positive symmetry indices) indicate leftward asymmetry; italicized numbers (and negative asymmetry indices) indicate rightward asymmetry. *Structures with significant asymmetry ($P < 0.05$).

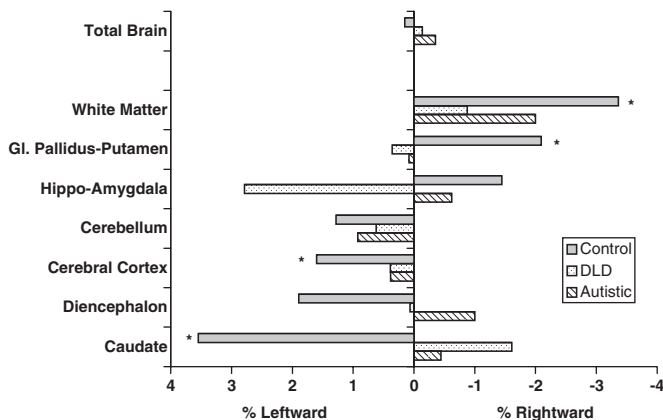


Fig. 3 Asymmetries of segmented structures. The x axis indicates percentage asymmetry to the left or the right. *Asymmetry is significantly different from zero.

classifications based on one-sample t tests were examined, only the frontal lobe cortex was significantly asymmetrical in controls (leftward, $P = 0.009$), but no lobes were significantly asymmetrical in either autism or DLD (Table 1).

Aggregate volume of cortical parcellation units with significant asymmetry

The total number of cortical PUs with significant asymmetry in either direction was 14 in the autism group, 15 in DLD, and eight in controls (Table 3). When the volumes of asymmetrical PUs were aggregated by group, the autistic series had a greater percentage of cortical volume (41.7%) with any significant asymmetry than did either boys with DLD (32.6%, $P < 0.0001$) or the controls (20.1%, $P < 0.0001$). Furthermore, the total percentage of cortical volume with significant asymmetry in DLD boys was also larger than in controls

($P < 0.0001$). Anatomical units with significant asymmetry are highlighted in Table 2 and are shaded in Fig. 2.

Aggregate volume and ratios of cortical parcellation units with significant leftward or rightward asymmetry

The numbers of directionally significant PUs were 10 right/4 left for autism, 9 right/6 left for DLD and 4 right/4 left for controls (Table 3). The autistic sample showed a significantly greater aggregate volume of right-asymmetrical cerebral cortex (28%) compared with both DLD (22%, $P < 0.0001$) and controls (7%, $P < 0.0001$) (Fig. 4A). The aggregate volume of right-asymmetrical cerebral cortex in DLD was also significantly larger than in controls ($P < 0.0001$). However, the DLD sample showed a reduction in the aggregate volume of left-asymmetrical cerebral cortex (11%) compared with both the autism group (14%, $P < 0.001$) and the control group (13%, $P < 0.001$), while a significant difference in the volumes of left-asymmetrical cortex between the autistic and control boys was not discerned ($P = 0.3$). The ratio of total right-asymmetrical cortical volume to total left-asymmetrical cortical volume was 1.8 in autism and 2.1 in DLD, but 0.38 in controls (Fig. 4B).

Comparisons of cortical parcellation units by processing type

Significant omnibus differences were found between autistic, DLD and control boys for asymmetry in unimodal PUs [$F(34,42) = 2.2$, $P = 0.007$] and in higher-order PUs [$F(34,42) = 3.4$, $P = 0.0001$] (Table 2). No significant differences in asymmetry of primary sensory and motor PUs were detected between the three groups [$F(12,42) = 0.73$, $P = 0.71$]. For individual unimodal and higher-order PUs, *post hoc* assessment of between-group differences is detailed in Table 4.

Comparison of language-related cortical parcellation units

A GLM-CD showed significant overall differences between autistic, DLD and control boys regarding asymmetry in language-related cortical areas [$F(11,42) = 2.31$, $P = 0.0097$]. The details of *post hoc* comparisons are included in Table 4.

Comparison of parcellation units by processing type excluding language parcellation units

When language-related PUs were removed from the two significant models, the omnibus group difference was no longer significant for unimodal PUs [$F(22,42) = 0.97$, $P = 0.52$], while the overall group difference remained significant for higher-order PUs, albeit to a lesser degree of significance [$F(22,42) = 1.96$, $P = 0.03$].

Table 2 Asymmetry of parcellation units by processing type (primary sensory and motor cortex, unimodal association cortex, higher order association cortex, and unclassifiable in this scheme)

Cortical Parcellation Unit	PU Code	Lobe	Language	Mean SI with Direction		
				Autistic	DLD	Control
PRIMARY SENSORY AND MOTOR CORTEX; $P = 0.71$.						
Central Operculum	CO	Frontal		22.29*	8.37	15.34
Precentral Gyrus	PRG	Frontal		6.18	4.12	0.74
Intracalcarine Cortex	CALC	Occipital		1.50	-7.07	-5.53
Supracalcarine Cortex	SCLC	Occipital		-7.88	-23.87	-20.93*
Postcentral Gyrus	POG	Parietal		8.35	4.20	15.57*
Heschl's Gyrus	H1	Temporal		13.81	15.20	11.93
UNIMODAL ASSOCIATION CORTEX; $P = 0.007$ ($P = 0.52$ w/o language-associated PU)						
Pars opercularis	F3o	Frontal	Language	-27.25*	-8.10	17.03
Frontal Operculum	FO	Frontal	Language	3.16	7.11	17.65*
Sup. Motor Cortex	SMC	Frontal		0.34	5.05	7.65
Cuneal Cortex	CN	Occipital		-9.81	-13.67	-18.93*
Occipital Fusiform Gyrus	OF	Occipital		3.69	-9.53	-7.27
Inf. Lat. Occipital Cortex	OLi	Occipital		5.75	-2.47	4.87
Sup. Lat. Occipital Cortex	OLs	Occipital		5.13	7.80	3.07
Planum Temporale	PT	Temporal	Language	24.81*	24.80*	5.07
Ant. Sup. Temporal Gyrus	T1a	Temporal	Language	14.13	-32.40	23.73
Post. Sup. Temporal Gyrus	T1p	Temporal	Language	4.19	1.40	-6.20
Ant. Middle Temporal Gyrus	T2a	Temporal		9.50	-13.07	34.20
Post. Middle Temporal Gyrus	T2p	Temporal		3.81	13.53	1.67
Ant. Inf. Temporal Gyrus	T3a	Temporal		5.69	-10.80	18.20
Post. Inf. Temporal Gyrus	T3p	Temporal		15.44	20.93*	2.13
Middle Temporooccipital Gyrus	TO2	Temporal		-42.88*	-48.93*	-24.07*
Inf. Temporooccipital Gyrus	TO3	Temporal		-56.13*	-38.27*	-21.27
Temporooccipital Fusiform Gyrus	TOF	Temporal		-31.31*	-31.93*	-4.67
HIGHER-ORDER ASSOCIATION CORTEX; $P = 0.0001$ ($P = 0.031$ w/o language)						
Pars triangularis	F3t	Frontal	Language	17.77	-2.72	33.28*
Frontal Medial Cortex	FMC	Frontal		7.13	-5.54	-5.11
Orbitofrontal Cortex	FOC	Frontal		2.42	1.68	3.80
Frontal Pole	FP	Frontal		-8.46*	-8.53*	-4.79
Ant. Cingulate Gyrus	Cga	Frontal		-8.49	-16.96	-5.39
Paracingulate Gyrus	PAC	Frontal		-3.91	-2.89	-1.85
Subcallosal Cortex	SC	Frontal		-3.99	2.80	5.65
Post. Cingulate Gyrus	CGp	Parietal		-2.26	0.37	-0.62
Angular Gyrus	AG	Parietal	Language	-29.15*	-9.41	-45.19*
Parietal Operculum	PO	Parietal		17.37	15.85	1.92
Ant. Supramarginal Gyrus	SGa	Parietal	Language	33.01*	29.69*	17.02
Post. Supramarginal Gyrus	SGp	Parietal	Language	-38.62*	-57.49*	-2.30
Ant. Parahippocampal Gyrus	PHa	Temporal		-16.50*	-22.20*	-2.47
Post. Parahippocampal Gyrus	Php	Temporal		4.25	7.33	3.67
Insula	INS	Temporal	Language	4.88	1.40	0.87
Planum Polare	PP	Temporal	Language	0.94	-22.07*	12.00
Temporal Pole	TP	Temporal		5.13	17.40*	-0.93
Unclassifiable (i.e. each PU is associated with multiple types of processing)						
Sup. Frontal Gyrus	F1	Frontal		7.73*	13.10*	11.64*
Middle Frontal 2 Gyrus	F2	Frontal		8.30	6.07	0.91
Lingual Gyrus	LG	Occipital		-9.31*	-11.47*	-0.07
Occipital Pole	OP	Occipital		11.88	14.93	15.40
Precuneus	PCN	Parietal		-8.79*	-11.49*	-3.88
Sup. Parietal Lobule	SPL	Parietal		10.25	8.53	2.45
Ant. Temporal Fusiform	TFa	Temporal		10.75	-8.40	17.40
Post. Temporal Fusiform	TFp	Temporal		20.00	19.00*	6.20

Positive symmetry indices indicate leftward asymmetry; negative asymmetry indices indicate rightward asymmetry. Bold-face and italics indicate PU with p -values from t -test significantly different from zero. "Lobe" column indicates the lobar classification of each PU; "Language" column indicated those PU associated with language processing. PU codes correspond to those used in Figure 1.

Table 3 Parcellation unit total and directional asymmetry: number of asymmetrical PUs, volume of asymmetry, and percentage of cortical volume that is asymmetrical

	Number of PUs			Volume (ml)			Percentage of cortical volume		
	Autistic	DLD	Control	Autistic	DLD	Control	Autistic	DLD	Control
Total asymmetrical	14	15	8	310.5	233.2	148.1	41.7	32.6	20.1
Right-asymmetrical	10	9	4	205.0	158.1	49.5	27.5	22.1	6.7
Left-asymmetrical	4	6	4	105.5	75.1	98.7	14.2	10.5	13.4

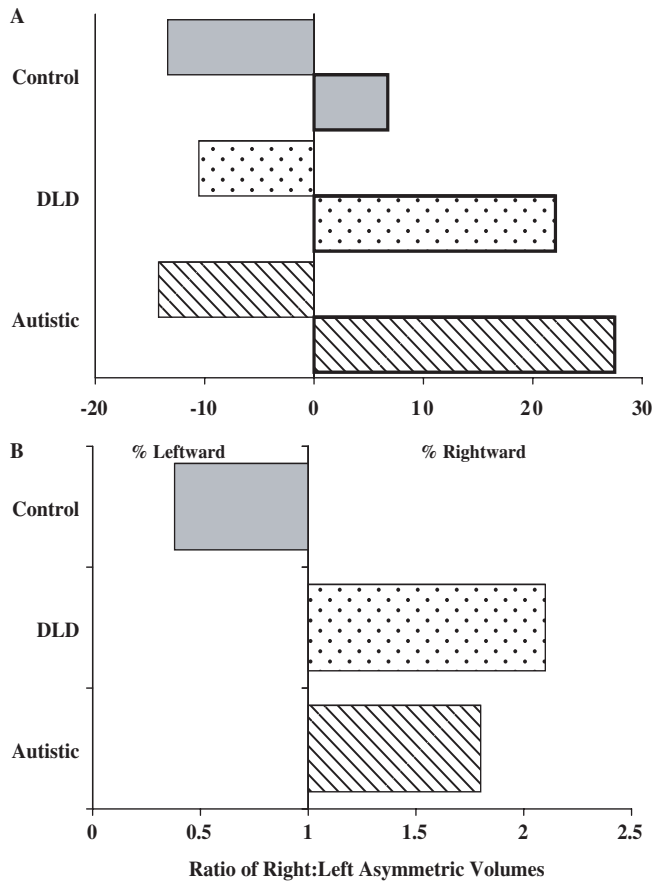


Fig. 4 (A) Percent of cortical volume with rightward or leftward asymmetry. Each bar reflects the total aggregated volume of cortical parcellation units that are significantly asymmetrical in the direction indicated on the *x* axis. The total percent of cortex asymmetrical in both directions is the sum of the two bars for each group; the DLD and autism groups have a larger volume of cortex with significant asymmetry than does the control group. (B) Ratios. Each bar represents the ratio of the total aggregated volume of right-asymmetric cortex to the total aggregated volume of left-asymmetric cortex. A ratio of 1 : 1 would indicate equal amounts of right- and left-asymmetric cortex.

Patterns of asymmetry across all units of parcellated cortex

Autistic and DLD boys showed significantly more similarities in patterns of symmetry and asymmetry when compared with each other than when either group was compared with

controls [$\chi^2(2) = 7.9, P = 0.02$]. As specified in the contingency table (Table 5), when autistic boys were compared with controls, 32 PUs were the same regarding symmetry or directional asymmetry, while 16 PUs were different. DLD and controls boys had the same pattern of symmetry or directional asymmetry in 29 PUs but were different in 19 PUs. However, boys with autism and DLD had the same patterns of symmetry or directional asymmetry in 41 PUs and were different for only seven PUs.

Discussion

In this whole-brain evaluation of cortical asymmetries in high-functioning boys with autism and DLD, the main findings are that patterns of cerebral symmetry are closely similar in the brains of autistic children and children with DLD, but differ substantially from brains of controls. Thus, in neither autism nor DLD is there asymmetry at the levels of major grey and white regions or the cerebral cortical lobes. However, nested within their overall and lobar cortical lack of asymmetry, in both autistic and DLD samples we see a substantial increase compared with controls in the aggregate amount of cortical PU asymmetry. In particular, right-asymmetrical cortex is substantially increased in autism and DLD; at the same time, while there is a decrease in the volume of left-asymmetrical cortex in DLD, there is no such loss relative to controls in the autistic brains. This leads to a similar reversal of the right : left cerebral cortex asymmetry ratio in the autistic and DLD samples compared with the controls.

Regarding the regional distribution of cortical asymmetry alterations, we found that there are significant differences among the groups in unimodal and higher-order association cortex, but not in primary sensory-motor cortex. Language-related cortical PUs appear to drive the differences at the level of unimodal association cortex, while higher-order association cortex differences are more robust, showing differences beyond those PUs considered to be related to language function. We also found that in their patterns of significant asymmetry throughout the cerebral cortex, boys with autism or DLD differed from controls but were very similar to each other.

These findings invite several observations. First, we see an intriguing disconnection in the asymmetry findings between the different levels of analysis, asymmetries being increasingly masked as the size of the units of analysis

Table 4 PUs in which autism and DLD differed from controls in the same and different ways

(A) PUs in which autism and DLD differed from controls in the same way				
	Loss of asymmetry in both autism and DLD		Gain of asymmetry in both autism and DLD	
	Left loss	Right loss	Left gain	Right gain
Unimodal	Frontal operculum (Lang)	Cuneal cortex	Planum temporale (Lang)	Inferior temporo-occipital gyrus Temporo-occipital fusiform gyrus Frontal pole
Higher-order	Pars triangularis (Lang)		Anterior supramarginal gyrus (Lang)	Anterior parahippocampal gyrus Posterior supramarginal gyrus (Lang)
Other	Postcentral gyrus	Supracalcarine gyrus		Precuneus Lingual gyrus
(B) PUs in which autism and DLD differed from controls differently				
	Loss of asymmetry in only one group		Gain of asymmetry in only one group	
	Left loss	Right loss	Left gain	Right gain
Unimodal			Posterior inferior temporal gyrus—DLD	Pars opercularis (Lang)—AUT
Higher-order		Angular gyrus (Lang)—DLD	Temporal pole—DLD	Planum polare (Lang)—DLD
Other			Central operculum—AUT Posterior temporal fusiform—DLD	

PUs associated with language function are indicated by ‘Lang’.

Table 5 Comparison of asymmetry across all units of cortex: number of parcellation units (PUs) with same and different asymmetry between each of the three possible pairwise comparisons

	Autistic versus control	DLD versus control	Autistic versus DLD
Number same	32	29	41
Number different	16	19	7

For each of the 48 PUs, a PU was considered to have the same asymmetry between two groups only if both groups had the same significance (significant or not) and also—only if significant—the same directionality (leftward or rightward) for both groups. In cases where both PUs were not significantly asymmetrical, they were classified as ‘same’ without consideration of directionality. Autism and DLD were more similar to each other than either was to controls [$\chi^2(2) = 7.9, P = 0.02$].

increases. Secondly, while the increase in rightward asymmetry is in keeping with prior reported findings, the increase in total asymmetry of aggregated cortical PUs is different from the loss of asymmetry that has been commonly reported and that we have found at our larger-unit levels of analysis. Finally, the differences from controls are not only more pronounced in higher-order association areas but also for the most part the same in both autism and DLD groups. If the widespread atypical asymmetries found in these two disorders were not so similar, the perturbations outside of language areas might be dismissed as random, or as ‘fluctuating asymmetry’ (Rasmuson, 2002). That the two samples are so similar not only implies a relationship between these

disorders, but also suggests that these changes reflect systematic and similar alterations in neural systems. The widely distributed significant asymmetry shifts in these two groups of brains may also indicate that meaningful asymmetries are widespread in the cerebral cortex.

Overall asymmetry: loss or rightward shift?

The loss of overall asymmetry of total cerebral cortex in autism and DLD, as measured by grey–white segmentation, may in fact be consistent with the gain in aggregate asymmetry of the cerebral cortex when it is subdivided into PUs. The autism and DLD brains showed an increase in the number (and volume) of cortical PUs with rightward asymmetry, but at the same time they showed either no loss (autism) or only a small loss (DLD) in the number (and volume) of cortical PUs with leftward asymmetry. The combined effect appears to be that the increase in rightward cortical asymmetry in autism and DLD has cancelled out the leftward asymmetry, so that the cortex taken as a whole (in the segmentation measure) appears symmetrical.

This apparent inconsistency between globally and regionally derived measures of overall asymmetry has methodological implications. It suggests that a lack of asymmetry in a large area may conceal non-uniform distributions of asymmetries within that area. Thus, interpretation of asymmetry data needs to take account of the level in the nested hierarchy of anatomical structures from which the units of analysis are drawn, and generalizations beyond that level may be inappropriate.

A large-scale rightward shift in autism and a childhood speech disorder (dysphasia) has been reported previously in two functional studies. Resting regional cerebral blood flow asymmetry was shifted from predominantly left to predominantly right in both an autistic (Chiron *et al.*, 1995) and a dysphasic group (Chiron *et al.*, 1999). However, this ratio shift had a different origin in each group. In the autism group this reversal of the right : left ratio was driven by regional cerebral blood flow that was no different from controls on the right but diminished on the left, while in the dysphasia group the left regional cerebral blood flow was largely unchanged while the right was increased. There thus appears to be less overall cerebral blood flow in the autistic sample and more in the dysphasic one. In the findings we currently report, the shift in right : left ratios of volume asymmetry is driven wholly in autism and predominantly in DLD by an increase in aggregate volume of asymmetrical PUs on the right. If the volume asymmetries similar to the ones we report here were present in subjects from both groups in the studies by Chiron, this would suggest that volume and metabolic rates have a different relationship in dysphasia than in autism.

Asymmetry in context: related to brain volume increase?

Neocortical asymmetry appears to be related to both interhemispheric connectivity and overall brain volume. In comparative studies, larger brain volume is associated with increased specialization and lateralization of function (Ringo, 1991; Rilling and Insel, 1999). One possible mechanism for this is that brain enlargement exacts a cost in the efficiency of interhemispheric connectivity which favours lateralized specialization (Ringo *et al.*, 1994). In addition, as brain volume increases, studies have shown that corpus callosum volume does not increase at the same rate (Jancke *et al.*, 1997). However, in our DLD and autism brains the disproportion is exaggerated: both groups show no increase at all in corpus callosum size, and in the case of autism there is a trend towards a decrease (Herbert *et al.*, 2004). Smaller corpus callosum volume has previously been documented in autism (Hardan *et al.*, 2000; Piven *et al.*, 1997; Egaas *et al.*, 1995), although not in DLD (Preis *et al.*, 2000). In addition, a callosal transfer deficit has been documented both in children with DLD (Fabbro *et al.*, 2002) and in children with autism (Nyden *et al.*, 2004).

Since the bulk of interhemispheric cortical communication relies on information transfer via the corpus callosum (Hopkins and Rilling, 2000), these larger brains with their disproportionately smaller corpus callosum sizes may experience greater than normal constraints on interhemispheric transfer of information via the corpus callosum. These extra constraints from both increased volume and lack of proportional increase in corpus callosum favour increased lateralization of processing, leading to greater asymmetry of neural activity and of volume (Zheng and

Purves, 1995). Moreover, the white matter volume increase driving the larger total brain volumes in autism and DLD shows a regional bias, with larger radiate white matter and a sparing of deep white matter (Herbert *et al.*, 2004); this may mean that intrahemispheric corticocortical fibres are increased while interhemispheric connections are not. This possible disproportionate increase in intrahemispheric connections, along with a bottleneck in interhemispheric linkages, should further increase the likelihood of functional lateralization and anatomical asymmetry.

Higher-order association areas, connectivity, and functional abnormalities

Widespread abnormalities in white matter, connectivity and asymmetry may relate to the functional abnormalities in autism and DLD, but because we do not understand the mechanisms by which these anatomical changes may exert their functional impacts, we do not assume that there is a direct correlation between the magnitude of anatomical changes and the magnitude of functional impact. In DLD, where asymmetry in language regions has received greater study, the existence or magnitude of asymmetry has not correlated consistently with diagnosis (Gauger *et al.*, 1997; Preis *et al.*, 1998). In the face of more widespread asymmetry abnormalities that go beyond regions associated with the deficits specifically characterizing either disorder, formulating the possible significance of such widespread changes would minimally require systematic correlation with behavioural data that goes beyond the scope of this paper. However, we would argue that it also and more fundamentally requires going beneath the defining behavioural features of the disorders.

From a cognitive neuroscience vantage point, the behaviours and deficits that define autism and DLD may be surface manifestations of underlying processing abnormalities (Morton and Frith, 1995; Belmonte *et al.*, 2004). It has been proposed that the features of the autistic behavioural phenotype emerge from an underlying deficit that can be characterized as 'weak central coherence' (Shah and Frith, 1993) or a 'generalized impairment in complex processing' (Minschew *et al.*, 1997), and that the language as well as the wide-ranging though subtle non-language impairments (Bishop, 2002; Kail, 1994) in DLD may arise from an underlying pervasive processing disorder (Kail, 1994; Johnston *et al.*, 1997). While the presence of language abnormalities in both disorders and the behavioural and social interaction impairments additionally found in autism (American Psychiatric Association, 1994; Rapin and Dunn, 2003; Rapin *et al.*, 2003) have invited a search for underlying focal brain abnormalities, the regional anatomical abnormalities that have been reported are not consistently replicated, while increased brain volume, which has been found frequently, challenges modular approaches to structure–function correlation (Herbert, in press). It may be that volume and white matter increases are anatomical correlates of underlying processing abnormalities. The tissue abnormalities leading to

increased white matter volume could lead to suboptimal connectivity, and this could in turn lead to poor coordination among individual components of neural circuits, resulting in pervasive processing abnormalities (Just *et al.*, 2004). Because higher-order associational activity involves greater integration than unimodal associational processing, areas with greater interconnections would, in this model, have heightened vulnerability to connectivity abnormalities.

Cortical areas related to language function are embedded in the unimodal and higher-order association areas that showed significant differences in our analysis. It may thus be the case that language functions are not specifically targeted by the underlying pathogenesis in either disorder, but rather are prominently affected because they are so highly reliant on associational processing (Mesulam, 1998). It may also be the case that the functions of social interaction and behaviour additionally impaired in autism are similarly vulnerable because of their dependence on complex associational processing. If this is the case, then since the behavioural abnormalities would eventuate from systems perturbations rather than only from focal disturbances, the magnitude of asymmetries in individual PUs may be less salient regarding functional significance.

Development of asymmetry and epigenetics

Association areas may have an additional source of vulnerability. They may be subject to greater epigenetic modulation because associational functions may develop later than primary functions and would thus be more experience-related (Luna *et al.*, 2001; Goldman-Rakic, 1988). They are especially unlikely to be under the control of one or two genes, but rather will be shaped in an activity-dependent fashion by a complex interaction of multiple genes and epigenetic factors (Kingsbury and Finlay, 2001; Krubitzer and Kahn, 2003). These asymmetries may thus help illuminate the developmental vulnerability of neural systems.

There is a further temporal component of vulnerability: the brain and white matter enlargement found in both groups appears to occur substantially postnatally. This postnatal growth pattern has been documented for autism (Lainhart *et al.*, 1997; Courchesne *et al.*, 2003), and it may be inferred for DLD as well, since in both the autism and DLD samples, white matter enlargement is not only present (Herbert *et al.*, 2003a, b) but is greater in areas that myelinate later (Herbert *et al.*, 2004). These abnormal volumes and growth trajectories may create pressures towards asymmetry that amplify over time.

Thus, while the increased number of cortical regions with rightward asymmetry may have significant consequences in terms of altered functionality, this phenomenon may not be primary in terms of pathogenesis. Altered cortical asymmetries may instead emerge as a response or adaptation to an abnormal brain and white matter growth trajectory. While increased volume and its associated dysfunctional connectivity may together lead to greater lateralization, the

increased and aberrant lateralization may then further degrade the functioning of the cortical networks that already, due to white matter abnormalities, have suboptimal connectivity.

The asymmetry alterations we report, seen in the context of the volume changes they accompany, may thus be the consequence of a positive feedback loop: increased volume results from white matter tissue changes that may impair connectivity, favouring lateralization and local processing. Moreover, the volume increase itself may on its own create a bias towards lateralization. These two dynamics may in turn combine to promote a progressive divergence from the norm regarding functions requiring associational activity. Such divergence may lead to processing and localization that are dysfunctional, and that in turn feed back into and amplify the ongoing dynamics. Added to this mix, and perhaps driving it, at least in part, may be abnormal or noisy neuronal activity (Rubenstein and Merzenich, 2003) that our data cannot address.

Widespread asymmetry shifts: implications

While our multivariate analysis found that differences among the groups were most robust in higher-order association areas, our χ^2 analysis provided a lens into the pervasiveness of the asymmetry alterations, both in showing that they are widely similar between autism and DLD, and in showing that they go beyond our initial functional classifications. These widespread alterations in anatomical asymmetry suggest that neural systems disruption in these disorders is pervasive, rather than limited to functionally relevant circuits. In this light, the instances of atypical functional localization that have been documented, such as in autism where the fusiform face area may (Hadjikhani *et al.*, 2004) or may not (Schultz *et al.*, 2000; Pierce *et al.*, 2001) activate normally for face processing, may actually be parts of more widespread but largely not yet identified neural systems abnormalities (Belmonte and Yurgelun-Todd, 2003; Hadjikhani *et al.*, 2004; Herbert *et al.*, 2004). The variable but common presence of additional non-language-based neurological and processing abnormalities such as clumsiness (Trauner *et al.*, 2000; Hill, 2001; Hardan *et al.*, 2003; Herbert *et al.*, 2003a, b; Rubenstein and Merzenich, 2003), often seen in these two groups, may be further consequences of these widespread abnormalities, and in that light not purely coincidental. Given these anatomical and processing abnormalities, one would predict that functional imaging or electrophysiological measures sensitive to altered timing would find reduced coordination among regions. This has been addressed theoretically (Brock *et al.*, 2002) and documented in a few metabolic and functional studies in autism (Horwitz *et al.*, 1988; Belmonte and Yurgelun-Todd 2003; Castelli *et al.*, 2002; Luna *et al.*, 2002).

The microanatomical underpinnings of grossly measurable cortical asymmetries have been the subject of an increasing body of research, but these studies have mainly focused on language regions, where differences in cytoarchitectural organization appear to be related to asymmetries in cortical processing capacities (Anderson *et al.*, 1999; Hutsler, 2003;

Hutsler and Galuske, 2003). Our findings demonstrate asymmetries in cortical PUs that are not only widely but also similarly (and hence probably systematically) distributed throughout the brain in two separate samples. This may suggest functionally meaningful hemispheric differences in cortical microstructure in brain regions other than those that are associated with language. Even though these increased and shifted asymmetries could also be dysfunctional (Escalante-Mead *et al.*, 2003), their apparent systematic distribution remains of interest.

Similarities between autism and DLD

While this study was designed to address comparisons at levels above the individual PUs, *post hoc* analyses revealed a few differences between autism and DLD at the level of individual PUs, although no frank reversals of significant asymmetry are found in any of our comparisons. We believe that it is premature to interrogate the *post hoc* findings regarding individual PUs for specific anatomical differences between autism and DLD, although they may provide suggestions for future studies. The fact that, in spite of such apparent differences, our autism and DLD samples share not only common patterns of altered asymmetry but also previously reported similar brain and white matter enlargement (Herbert *et al.*, 2003a, b) strongly supports attending to these common morphometric features. One important weakness of this study is the absence of IQ data for the controls, which may confound the ways that controls differ from the other two groups. Nevertheless, the fact remains that the autism and DLD groups themselves have no significant IQ differences that might confound the multiple similarities we have detected between them.

There are theoretical reasons for the importance of looking at similarities among developmental disorders (Johnson *et al.*, 2002) that encompass a number of concerns (Karmiloff-Smith, 1998). For one thing, these disorders do not appear to be discretely distinct from each other in their phenotypes, but rather to show considerable overlap (Bishop, 1989; Howlin *et al.*, 2000; Rapin and Dunn, 2003). Secondly, there is considerable heterogeneity in many phenotypic features within each disorder (Brzustowicz, 1998; Buxbaum *et al.*, 2001; Felsenfeld, 2002; Yonan *et al.*, 2003). Thirdly, genetic investigations to date have not uncovered evidence of a small number of genes each with considerable influence and power to shape phenotype; while this might be a function of insufficient power to demonstrate linkage, it might also suggest that a larger number of genes may be involved, with pleiotropy and with each having a modest role that is more modulatory than determinative. The overall picture is probably one of a complex interaction of genes and non-genetic factors to produce a risk of abnormality and a spectrum of phenotypic presentations (Hyman, 2000; Bishop, 2001). Our findings of considerable morphometric similarity between DLD and autism at multiple levels are thus consistent with developments in research on both genotype and behavioural phenotype.

Conclusion

Our examination of asymmetry at multiple levels has yielded findings of similarly increased aggregate and rightward cerebral cortical asymmetry in high-functioning autism and DLD. These findings may be related to the large-scale volume changes found in the same brains, which are likely to affect inter-regional connectivity, but differently within hemispheres compared with between hemispheres. Connectivity alterations may preferentially affect higher-order association areas that have more interaction among neural systems components. While we do not know how much these findings extend into the lower-functioning autistic population, this merits exploration.

Our findings of widespread shifts in cortical asymmetry in both high-functioning autism and DLD suggest that the anatomical changes underlying these disorders are pervasive. It follows from this that functional deficits may be relatively pervasive as well, although they may manifest in different domains with different degrees of severity. Some functions may be more vulnerable to these anatomical changes than others, and performance on other tasks may be essentially normal. Moreover, the link between pathogenic mechanisms and functional manifestations may be indirect or related to systems dysfunction. Aberrant asymmetry, including both focal and widespread alterations, may be functionally important but epigenetically downstream consequences of pervasive volume, tissue and neurochemical alterations. Future research needs to explore the nature and implications of these structural and functional alterations, including their pervasive and systematically similar character in the two disorders, their relationship to processing, and the underlying tissue changes and potential causative mechanisms.

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