Localization of White Matter Volume Increase in Autism and Developmental Language Disorder

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Increased brain volume in autism appears to be driven mainly by an unexplained white matter enlargement, and we have reported a similar phenomenon in developmental language disorder (DLD). Localization of this enlargement would strongly guide research into its cause, tissue basis, and functional implications. We utilized a white matter parcellation technique that divides cerebral white matter into an outer zone containing the radiate compartment and an inner zone containing sagittal and bridging system compartments. In both high-functioning autism and DLD, enlargement localized to the radiate white matter (all lobes in autism, all but parietal in DLD), whereas inner zone white matter compartments showed no volume differences from controls. Furthermore, in both autism and DLD, later or longer-myelinating regions showed greater volume increases over controls. Neither group showed cerebral cortex, corpus callosum, or internal capsule volume differences from control. Radiate white matter myelinates later than deep white matter; this pattern of enlargement thus is consistent with striking postnatal head circumference percentile increases reported in autism. These findings suggest an ongoing postnatal process in both autism and DLD that is probably intrinsic to white matter, that primarily affects intrahemispheric and corticocortical connections, and that places these two disorders on the same spectrum.

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Autism and developmental language disorder (DLD) both are phenotypically defined developmental neurobehavioral disorders. Although both disorders involve impairments in the language domain,[1] in autism there is additional marked impairment in social interaction, as well as interests and behavior that are narrow, repetitive, or ritualistic.[2] At the same time, both disorders affect male more than female subjects, and both are associated with a variably expressed set of secondary features that include seizures as well as sensory, motor, and other impairments, although the relationships of these features to the primary diagnoses are not understood.[3,4]

To date, no reliable biomarker has been discovered for either autism or DLD. However, among autistic subjects one of the most replicated neuroanatomical findings is a tendency for brains to be large, particularly among younger subjects.[5–7] This increase also has an unusual developmental trajectory: head circumference is normal or even somewhat small at birth and increases precipitously over several standard deviations during the first few years of life.[7,8] This brain volume increase appears predominantly caused by abnormally large white matter volume.[6,9–11]

Among DLD subjects, total brain volume has rarely been measured. Two studies showed unchanged to slightly decreased brain volume,[12,13] whereas two, including our own, showed volume increase.[6,14,15] In our DLD sample, this brain volume increase is also, as in autism, primarily caused by a volume increase in white matter.[15]

Studies to date have considered white matter as either a uniform compartment or divided only into lobes. Our investigation used magnetic resonance im-

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aging–based methods that subdivide white matter by parcellating it both regionally by lobes and radially for fiber system subcompartments.[16–20] Based on contiguity to cortical and subcortical anatomic landmarks identified during prior segmentation and cortical parcellation,[21] it topographically divides the white matter into parcellation units whose boundaries relate to white matter fiber pathways. The anatomic distinctions of our white matter parcellation approach thus approximately correlate with different neural systems and their relative developmental epochs of maturation. We thus expected that the phenotypic distinctiveness of autism and DLD also would be apparent in features of neural systems that this morphometric method discerns.

Subjects and Methods

Subjects

Quantitative volumetric analysis was performed on brain magnetic resonance images of 41 boys (13 autistic, 14 DLD, 14 normal control) and 22 girls (7 DLD, 15 normal controls), 5.7 to 11.3 years of age. Mean age at scanning was 9.0 ± 0.9 years (autistic), 8.2 ±1.6 years (DLD), and 9.1 ±1.2 years (controls). All autistic and DLD subjects had performance IQs greater than 80. Autistic and DLD children were recruited as part of a larger study of children with disorders of communication, conducted between 1985 and 1988, by clinical referral or participation in school special needs programs.[22] Control subjects were recruited specifically for imaging purposes; eligibility required normal developmental history without seizures or significant head injury, normal school performance, and normal neurological examination.[23] English was the primary language of each child's family. Exclusionary criteria included hearing or gross sensorimotor deficits; clinical progressive encephalopathy; frequent seizures; 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 analyzed in this study were judged by a clinical neuroradiologist 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

Diagnostic instruments meeting standards at the time the study was conducted were used for classification as autistic or language impaired, and expert clinicians confirmed all diagnoses. All children were screened using the three-part Wing Autistic Disorder Interview Checklist (WADIC),[22] which was a parent questionnaire reviewed with an investigator or trained research assistant covering (1) impairment in social relatedness (nine questions), (2) impairment in social communication (five questions), and (3) restricted or repetitive activities (seven questions). If the child either (1) met at least one criterion from each of three sections of the WADIC; or (2) met two criteria from the first section of this interview checklist, then the child was provisionally classified as possibly autistic. Absolute criteria from the WADIC screen for inclusion in the autistic group comprised meeting three criteria in the first set, three in the second, and one in the third. All children were confirmed or disconfirmed in their diagnosis by a child psychiatrist blinded to prior stages of diagnosis who performed a structured comprehensive evaluation with determination of diagnosis according to Diagnostic and Statistical Manual III-R criteria that were current at the time.

In the original study, children who failed to meet criteria for autism, and whose nonverbal IQ scores were above 80, then were screened for DLD. DLD classification required significant relative deficiency in language measures, meaning either (1) a score on the Test of Early Language Development[24] 1 SD below the mean NVIQ score, or (2) a mean length of utterance score 1 SD below the mean for the child's chronological age.

Image Acquisition

Magnetic resonance imaging was performed on either General Electric 1.5 T Signa (Milwaukee, WI) or Siemens 1.5 T Magnetom (Iselin, NJ) magnetic resonance imaging systems. Images, acquired between 1989 and 1992, included a T1-weighted sagittal scout series, a coronal T2-weighted sequence to rule out overt focal lesions, and a coronal volumetric T1-weighted spoiled gradient-echo imaging sequence for the morphometric analysis. GE volumetric parameters were pulse sequence, 3D-SPGR or 3D-CAPRY; TR, 34 to 50 milliseconds; TE, 5 to 9 milliseconds; flip angle, 45 to 50 degrees; field of view, 24 to 26cm; slice thickness, 3.0 to 3.1mm; number of slices, 60 contiguous; matrix, 256 × 256; number of excitations, 1. On Siemens systems, volumetric parameters were pulse sequence, 3D-FLASH; TR, 40 milliseconds; TE, 10 milliseconds; flip angle, 40 degrees; field of view, 30 cm; slice thickness, 3.1mm, number of slices, 60 contiguous; matrix, 256 × 256, number of excitations, 1. Intercenter calibration for comparable contrast was followed by a phantom study confirming that images on the two systems were comparable for quantitative segmentation analysis.[25] To further ensure that the use of multiple imaging systems was not a confounding factor, scanner type was included as a covariate in all statistical analyses.

Image Positional Normalization

Imaging data were analyzed on Sun Microsystems (Mountainview, CA) workstations. The initial image data set was normalized with respect to Talairach stereotactic space.[26] Coronal, axial, and sagittal planes used in the morphometric algorithms then were derived computationally.

Image Analysis

Neuroanatomic segmentation was performed using semiautomated algorithms based on intensity contour mapping and differential intensity contour algorithms previously described (Fig 1A).[18] Segmentation, performed on coronal images, divided the brain into gray matter and white matter subdivisions. Cerebral cortex–white matter distinctions were accomplished in a semiautomated fashion, whereas deep gray nuclei were delineated manually. Cortical parcellation was performed manually.[19,20]

White matter parcellation (see Fig 1B–D) is a virtually automatic comprehensive parcellation of the human cerebral white matter.[16,17] It is performed algorithmically, based on

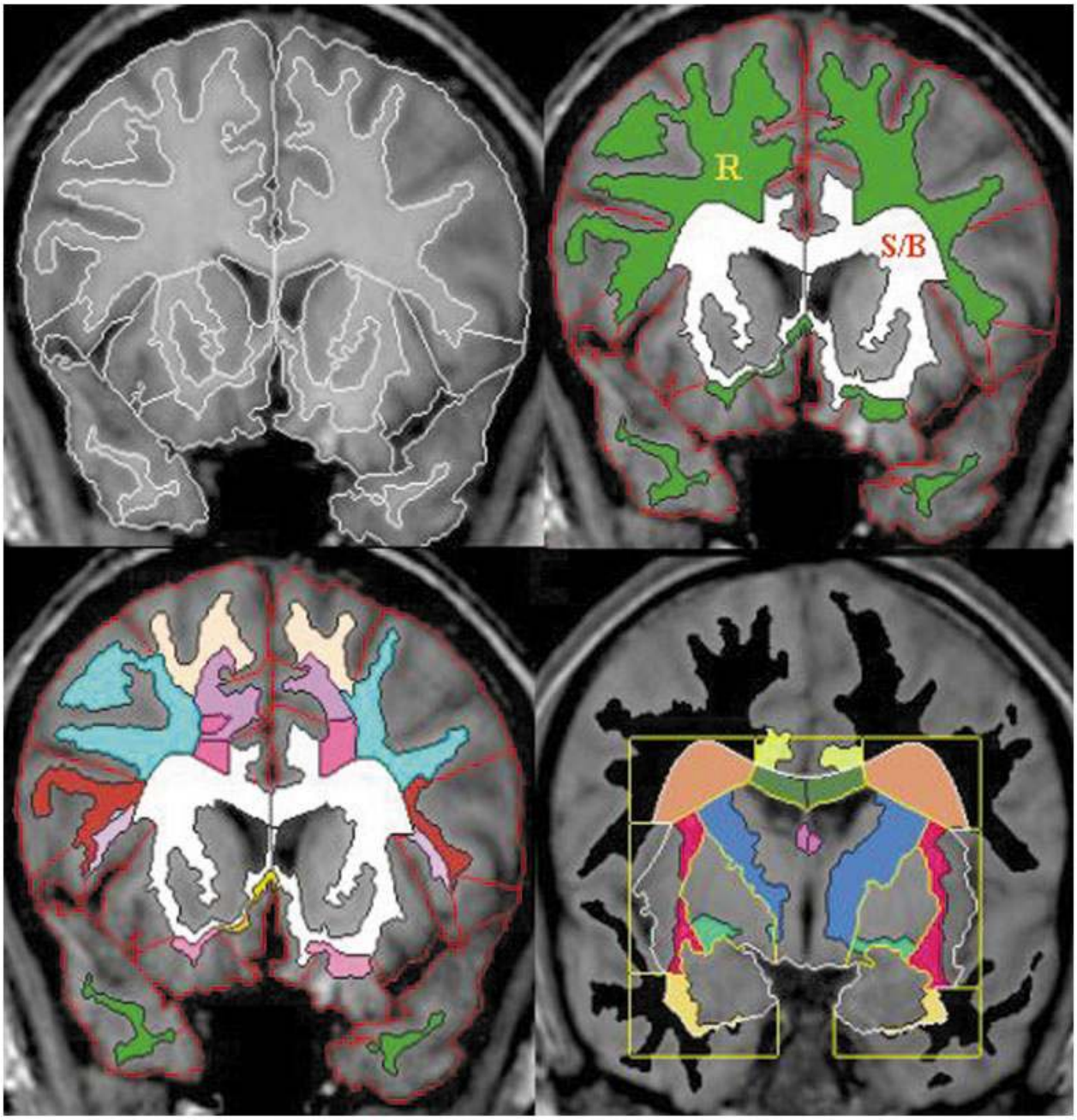

Fig 1. Cerebral white matter parcellation. (A) Gray-white segmentation. (B) Initial division of white matter into outer and inner zones. (C) Parcellation of radiate (R) compartment. (D) Parcellation of sagittal and bridging (S/B) systems compartments.

boundaries delineated by prior segmentation[18] and parcellation,[19] after the addition of six manually identified points in the corpus callosum and deep gray matter.[16,17] Interrater reliability has been reported for cortical parcellation,[20] and, because the generation of white matter parcellation boundaries are created as automated, topographic constructs, virtually no additional interrater variability is introduced by this procedure. Although white matter tracts are not visible in the T1-weighted scans typically parcellated, the tract system was used as the basis for the algorithmic white matter parcellation rules.

White matter parcellation divides the white matter into three compartments: radiate, sagittal, and bridging.[17] (1) The radiate compartment corresponds partly to the corona radiata, but also includes the "unnamed fibers"[27] or U-fibers, and also fibers that border the sagittal compartment; it encompasses essentially the full extent of subcortical white matter excepting that subjacent to the insular cortex. (2) The sagittal compartment consists of three sets of fibers: (a) ipsilateral association fiber systems, (b) the projection fibers linking cortex, thalamus, and basal ganglia, including both amygdala and cortical projections to the pons and spinal

cord, and (c) intrahemispheric extension of callosal fibers. The first two groups run approximately in the sagittal plane, whereas the third is indistinguishable from the first two on magnetic resonance images. The sagittal compartment includes six classically defined associative fasciculi: the superior longitudinal (arcuate) fasciculus, the inferior longitudinal fasciculus, the uncinate fasciculus, the extreme capsule, the cingulum bundle, and the occipitofrontal fasciculus. (3) The bridging systems compartment consists of (a) commissural fibers including corpus callosum, anterior commissure, and dorsal and ventral hippocampal commissures, and (b) the internal capsule and basal forebrain system.

The parcellation of white matter proceeds in two stages.[16] First, cerebral white matter is divided into outer and inner zones (see Fig 1B) on an automated voxel-by-voxel basis according to distance from cortical and subcortical gray matter. The outer zone contains the radiate compartment, and the inner zone consists of the sagittal and bridging compartments. Second, these two zones are parcellated. The outer zone is parcellated by proximity to overlying cortical PU (see Fig 1C). Both the sagittal and bridging compartments that comprise the inner zone are subdivided into individual fascicular divisions (see Fig 1D) which are further parcellated into smaller, anterior-posterior ordered parcellation units (white matter PUs). The total number of voxels in each PU determines its volume (Table 1). To constrain the number of statistical comparisons, we grouped radiate PUs by lobe and sagittal/bridging PUs into their major fiber systems (see Table 1).

Data Analysis

SPSS (SPSS, Chicago, IL) and SAS (SAS Institute, Cary, NC) were used for statistical computations. Multivariate general linear models for correlated data[28] were used for overall comparisons, with age and scanner included as covariates, because the data were found to be approximately normally distributed and because neuroanatomical constraints involve high correlations between some brain regions. Autistic and DLD subjects were compared with controls separately, because no female autistic subjects were included in this study. For comparisons of DLD to control subjects, initial models included a sex by diagnosis term, with age and scanner as covariates. If no significant interaction was found, the model was repeated without the interaction term, with age, scanner, and sex as covariates. Post hoc analyses utilized univariate GLMs, with age and scanner as covariates for autistic by control comparisons, and with the addition of sex for DLD by control comparisons. Polynomial regression was used to explore relationships between age and total radiate and sagittal/bridging volumes in each of the groups. For comparisons of autistic to other subjects, only boys were included in the models, with age and scanner included as covariates.

Effect sizes[29] of the differences between groups were estimated for each region as follows: mean volume of Group A minus mean volume of Group B divided by the pooled standard deviation of Group A and B volumes. Effect sizes were computed for all pairwise comparisons (ie, autistic by control, DLD by control, and autistic by DLD).

We then performed post hoc exploratory analyses to examine volume differences as a function of the myelination sequence, assessing the relationship of white matter volume changes to the timing and duration of myelination in different brain areas. To do this, we utilized detailed documentation of myelin development from classic neuropathology studies regarding three temporal landmarks, measured in postconceptional weeks: (1) *myelination onset:* the week dur-

Table 1. Descriptive Statistics for White Matter Volumes

	Autistic Group (13 male subjects)		DLD Group (14 male, 7 female subjects)		Control Group (14 male, 15 female subjects)		Autistic × Control		DLD × Control		Autistic × DLD	
White Matter Division	Mean (ml)	SD	Mean (ml)	SD	Mean (ml)	SD	ES	t (26) significance	ES	t (47) significance	ES	t (33) significance
Total superficial	347.07	51.6	320.39	61.1	279.04	38.6	1.04	0.005	0.78	0.005	0.48	0.760
Frontal lobe	154.05	24.9	140.18	31.8	120.97	18.0	1.08	0.002	0.73	0.032	0.47	0.694
Prefrontal	62.36	13.26	57.6	15.37	45.82	8.36	1.98	0.004	1.41	0.002	0.31	0.740
Parietal lobe	76.27	10.7	65.83	13.1	63.72	9.6	0.80	0.016	0.19	0.438	0.80	0.448
Temporal lobe	53.82	11.5	51.97	9.7	43.09	7.6	0.82	0.022	0.93	0.024	0.18	0.676
Occipital lobe	62.94	14.0	62.42	15.3	51.25	11.0	0.71	0.048	0.80	0.020	0.04	0.640
Total deep	97.72	14.7	94.88	16.2	92.61	11.2	0.09	0.821	0.17	0.582	0.22	0.302
Corpus callosum	15.89	3.6	16.46	3.2	16.50	3.0	−0.50	0.181	−0.01	0.889	−0.17	0.103
Cingulum	12.79	2.1	12.71	3.1	11.07	2.2	0.67	0.070	0.60	0.050	0.03	0.377
Sup. sag. stratum	26.11	3.4	24.06	4.5	24.17	2.3	0.38	0.309	−0.03	0.620	0.49	0.759
Inf. sag. stratum	20.82	4.5	20.47	3.8	19.28	3.0	0.15	0.688	0.35	0.352	0.09	0.414
Temp. sag. stratum	2.86	0.5	2.72	0.5	2.45	0.7	0.57	0.120	0.43	0.211	0.28	0.705
Basal forebrain	2.41	0.7	2.24	0.8	2.82	0.7	−0.68	0.048	−0.76	0.024	0.23	0.783
Internal capsule	14.16	2.7	13.96	3.0	14.40	2.0	−0.44	0.234	−0.18	0.356	0.07	0.274

p values refer to post hoc univariate tests of regional volume differences while controlling for age, scanner, and, for the DLD by control comparisons, sex.
DLD = developmental language disorder; ES = (mean volume of group A) − (mean volume of group B)/pooled SD; M = male; F = female.

ing which myelination began for most subjects, (2) *myelination maturity:* the week in which mature myelin was found for at least 50% of infants studied, and (3) the *myelination interval:* the number of weeks between myelination onset and myelination maturity in greater than 50% of infants.[30–32] We selected 14 regions with good correspondence between our PU definitions and regions as defined neuropathologically.[30] For each white matter PU selected, we regressed volumes against the above three neuropathologically measured time points for that area (Table 2, Fig 2). For volumes in these regressions, we utilized *Z*-scores of volumes, standardized against control values: for each individual subject, we subtracted control mean volume from each individual's region volume and divided the result by the control standard deviation for that region. This procedure standardized volumes to the control means and standard deviations. Mean *Z*-scores then were calculated for each PU for the autistic and DLD groups separately (see Table 2). Polynomial regression was used to determine the best-fitting curve of the relationship between mean *Z*-scores and each of the three myelination timetable variables (see Fig 5). A Fisher *Z* transformation of the correlations was performed to test for differences in the best-fitting curves between autistic and DLD subjects.[33] Finally, stepwise multiple regression models were used to determine which of the myelogenetic cycle variables best predicted the *Z*-scores (representing the difference between the patient and control populations) for autistic and DLD subjects separately. The six variables included in the stepwise regression analyses included each time point and the square of each time point.

Results

We first compared total radiate compartment (outer zone) and total sagittal plus bridging compartment (deep zone) volumes (see Table 1, Fig 3) among groups. Compared with controls, the total radiate compartment of white matter was larger in both the autistic and DLD samples ($p = 0.005$ for each). However, the total combined volume of the sagittal and bridging compartments was not significantly different from controls in either the autistic ($p = 0.83$) or the DLD group ($p = 0.58$). Autistic and DLD brains, however, did not differ significantly regarding either total radiate compartment volume ($p = 0.55$) or total combined sagittal and bridging compartment volumes ($p = 0.54$). In addition, no significant linear or nonlinear relationships were found between age and radiate or sagittal/bridging volumes for any group.

We next subdivided the radiate compartment into lobar divisions and found that the radiate compartment volume increase was not entirely uniformly distributed. Moreover, this nonuniformity differed between autism and DLD. Significant omnibus differences from controls were found for the brains of both autistic ($F[12,26] = 5.3$, $p = 0.0002$) and DLD ($F[12,49] = 2.3$, $p = 0.02$) subjects. Although all lobes showed significant enlargement in the autistic group (see Table 1, Fig 3), the effect was particularly strong in the frontal lobe (27% increase, $p = 0.002$). In the DLD sample, the frontal lobe enlargement was present (16% increase, $p = 0.03$), but it was no greater than the enlargement of temporal (20%, $p = 0.02$) or occipital (22%, $p = 0.02$) lobes, and the parietal lobe was not enlarged. When autistic and DLD brains were compared, there was no significant omnibus difference ($F[11,13] = 0.69$, $p = 0.73$).

In the sagittal and bridging compartments, there were no differences between autism and DLD, and only a few regions differed significantly between the autistic or DLD and the control subjects. Basal forebrain was reduced in both autistic ($p = 0.048$) and DLD ($p = 0.02$) groups relative to controls, whereas cingulum bundle was marginally increased in volume

Table 2. Sequence and Duration of Myelination

Location	Autistic Mean *Z*-score	DLD Mean *Z*-score	Myelin Onset (weeks)	Myelin Maturity (weeks)	Myelination Interval (weeks)
Pos. internal capsule	−0.33	−0.38	38	44	6
Body of corpus	−0.13	0.18	50	60	10
Splenium of corpus	−1.36	−0.63	54	65	11
Postcentral gyrus	1.27	0.03	41	72	18
Calcarine	0.15	0.15	54	72	18
Precentral gyrus	0.81	0.17	41	70	29
Rostrum of corpus	−0.61	−0.11	57	87	30
Cingulum	0.66	0.75	47	80	33
Ant. Internal capsule	−0.59	0.19	50	87	37
Occipital pole	0.82	1.98	47	87	40
Heschl's gyrus	1.77	1.49	44	88	44
Frontal pole	1.21	1.37	50	119	69
Temporal pole	1.30	1.85	47	122	75

The *Z*-scores were derived for each individual subject and then averaged by group. The values for myelination onset, myelination maturity, and myelination interval are derived from Kinney and colleagues.[30]
DLD = developmental language disorder.

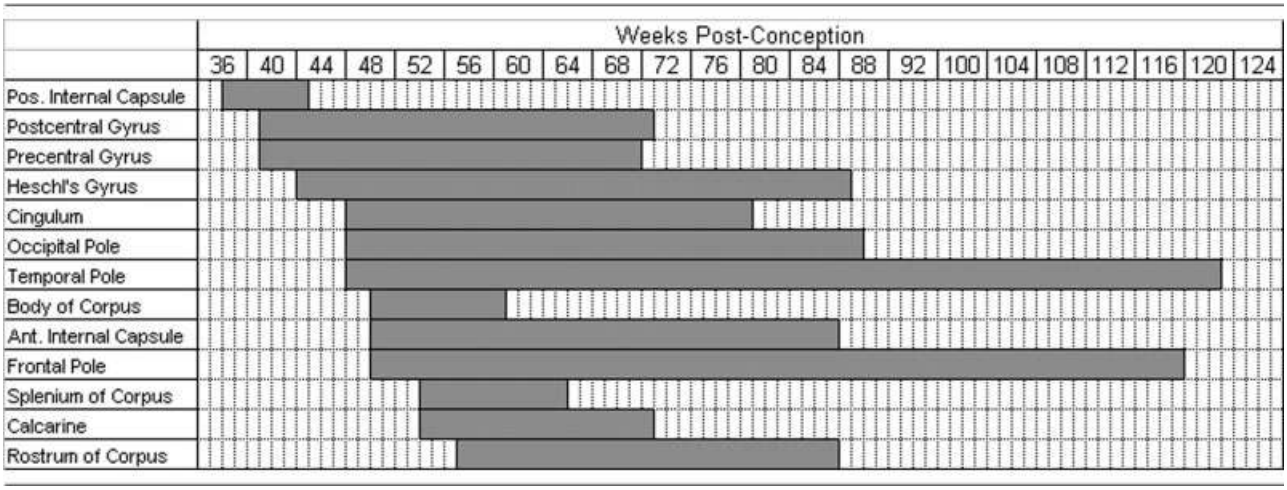

Fig 2. Myelination timetable for selected regions. Gray bars start with myelination onset *and end with* myelination maturity*, as defined in Kinney and colleagues[30] as the week when 50% of subjects meet maturity criteria. The length of the bar represents the* myelination interval.

as compared with controls in DLD ($p = 0.05$) brains, but not in autistic brains.

We next compared volumes of white matter PU encompassing prefrontal white matter, which is comprised almost entirely of intrahemispheric corticocortical fibers. Both autism and DLD showed greater differences compared with controls in prefrontal than in frontal or other lobar white matter: autistic boys were 36% larger ($p = 0.004$) and DLD boys 26% larger ($p = 0.002$) than controls (Fig 4).

Volume differences varied as a function of regional differences in timing of onset, duration, and maturation of myelination, using measures and regressions described in Subjects and Methods (see Fig 2). Of our three measures, the mean myelination interval, or length of time from myelination onset to myelin maturity, was most strongly related to the amount of volume increase over controls (Fig 5C). For both the autistic and DLD groups, the myelination interval showed a linear (first-order) relationship to mean *Z*-scores of volume increase over controls (autistic: $R^2 = 0.48$, $p = 0.008$; DLD: $R^2 = 0.67$, $p = 0.001$). The time of myelination onset also showed a strong relationship to volume increase for both groups, with nonlinear (second-order) relationships (see Fig 5A) for both the autistic ($R^2 = 0.55$, $p = 0.02$) and DLD ($R^2 = 0.51$, $p = 0.03$) groups. Our third variable, the time of myelination maturity, was also related to the amount of volume increase, with a linear (first-order) relationship to mean *Z*-scores (see Fig 5B) for both DLD ($R^2 = 0.51$, $p = 0.003$) and autistic subjects ($R^2 = 0.34$, $p = 0.04$). No significant differences in best-fitting lines were found between autistic and DLD subjects for any of the three myelination measures.

These findings of greater white matter volume increase in regions that myelinated later or for a longer time interval were further supported by stepwise regression. In the autistic group, a two-step model including myelination interval ($R^2 = 0.48$, $p = 0.001$) and the square of the time of myelination onset ($R^2 = 0.29$, $p = 0.015$) predicted 77% of the mean *Z*-score variance ($p = 0.001$). In the DLD group, a single-variable model provided the best fit, with myelination interval accounting for 67% of the mean *Z*-score variance ($p = 0.001$).

Discussion

Our investigation of the regional biases in white matter volume increase in these two disorders was motivated by our prior findings that white matter contributes disproportionately to an increase in total brain volume measured in both our autism and our DLD samples, whereas cerebral cortex in both groups shows no volume increase and in fact is proportionately smaller.[11,15]

We now report that this disproportionate white matter enlargement in high-functioning autism and DLD is nonuniformly distributed, being expressed almost exclusively in the radiate white matter compartment in both disorders. White matter in the sagittal and bridging compartments (deep zone), and in particular, the internal capsule and corpus callosum, shows no volume differences from controls in either group. In addition, in both autism and DLD, later or longer-myelinating regions show greater volume increase over controls. In all of these respects, the autism and DLD brains are largely the same. However, within the radiate compartment the two groups show regional differences: in the autism brains there is enlargement in all lobes but with a frontal predominance, whereas in the DLD brains the parietal lobe is spared the enlargement whereas the

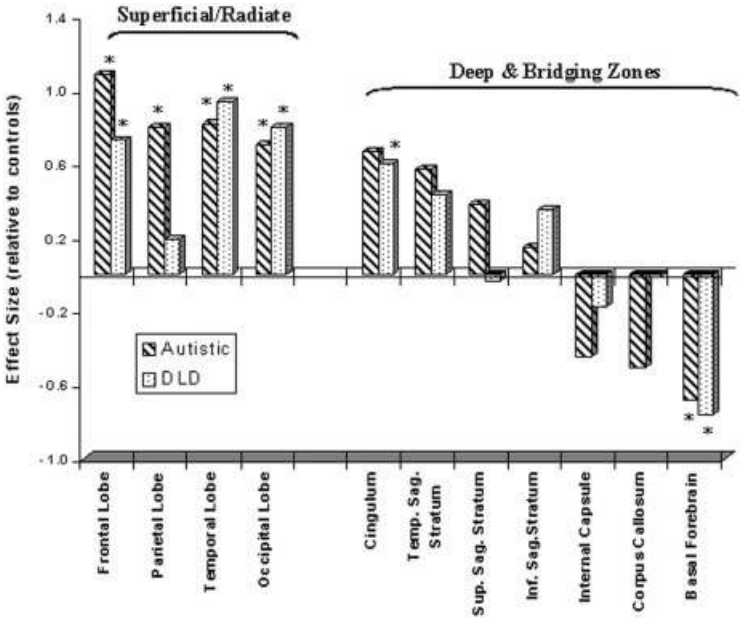

Fig 3. White matter volumes. Comparisons with controls are made in terms of effect sizes: mean volume of study group minus mean volume of controls divided by the pooled standard deviation of study group and control volumes. An asterisk indicates statistically significant difference. White matter regions are grouped by compartments, with the sagittal and bridging systems compartments comprising the inner zone grouped together.

volume increase is fairly uniform among the other three lobes. Yet in both groups, the most striking amount of volume increase is seen in the white matter underlying prefrontal cerebral cortex, although the increase is greater in the autism sample.

These findings, both robust and replicated in part by other investigators, conform readily to no established models for mechanisms either of pathogenesis or of anatomic substrate of behavioral dysfunction. Understanding their impact on function is dependent at least in part on tissue characterization of the volume change that would require fresh data. Of note, T2-weighted scans in these subjects did not show any white matter abnormalities. Our T1-weighted volumetric scans cannot, however, tell us whether this normal looking white matter is enlarged because of axonal increase, increased myelin-to-axon ratio, or an increase in other white matter components with unchanged quantities of myelin and axons. Nevertheless, the distribution of the volume changes offers a range of clues to their likely tissue microstructure basis, as well as to the developmental epoch in which these changes occur and to their possible functional implications.

Volumetrics and Developmental Timing

The central contribution of our findings is to offer a new spatiotemporal axis along which to characterize the nonuniformity of the white matter enlargement in these autism and DLD brains. The radiate compartment, to which the volume increase is confined, remains relatively unmyelinated until late in the first year of life,[32] with myelination continuing in the second year and even, in some regions, particularly frontal and prefrontal, later. We thus have discerned a volumetric dissociation of later-myelinating radiate compartment enlargement from unchanged earlier-myelinating deep zone sagittal and bridging compartment volumes. This radiate volumetric increase is most likely the footprint of a pathogenic process that in some way altered the development of later-myelinating white matter.

Our findings therefore are consistent with multiple studies showing that the brain volume increase in autism is postnatal. Retrospective head circumference studies of autistic children demonstrate increases in percentile as great as two standard deviations between birth and two years of age.[7,8] Indeed, by the time autistic children are 2 to 4 years old, 90% have above-average brain volumes and 37% are frankly macrocephalic.[9] And volumetric studies have shown unusually large total brain and white matter volumes in autistic 2 to 4 year olds.[9,10] The brain volumetric similarities that we have found between autism and DLD brains[6,11] suggest that similar studies should be performed with DLD children.

The regional analyses we performed based on myelination timetables add further support to our sense that the similar distribution of white matter volume changes in these two disorders reflects a strong temporal influence. Of the three myelination timetable measures we utilized, the duration of myelination showed the greatest positive correlation with the extent of volume increase over controls, but our other two myelination timetable measures, myelination onset and myelination maturity, were also positively correlated with greater white matter volume increases. The curvilinear nature of the correlation between myelination onset and volume differences suggests that, of those structures presently examined, those that begin to myelinate

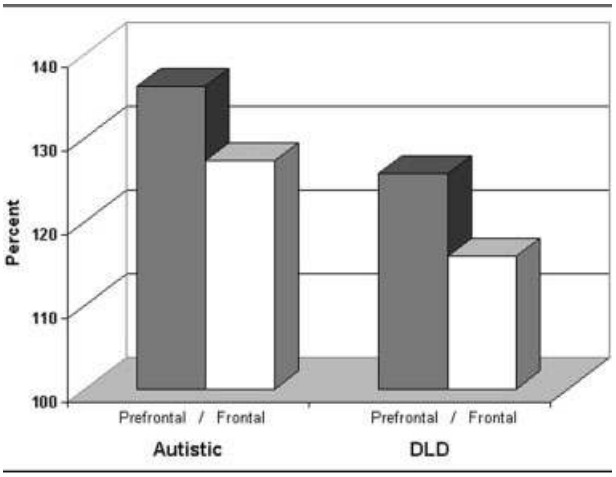

Fig 4. Prefrontal and frontal lobe white matter volumes. Volumes are presented as percentage of control volume. DLD = developmental language disorder.

very early or very late are less affected than those that fall in between. The thrust of these findings is that the white matter volume increases in both autism and DLD result from an ongoing process with cumulative effects that become stronger over time.

Volumetrics, Connections, and Tissue Changes

The volumetric dissociation of the enlarged radiate compartment from the unchanged sagittal and bridging compartments includes a lack of volume increase in either corpus callosum or internal capsule and has implications for the types of connections involved. This lack of expected association between radiate compartment and corpus callosum volume[34] suggests that the white matter volume increase predominantly involves short and medium-range corticocortical connections within hemispheres, with less, if any, involvement of connections between hemispheres. The dissociation between the radiate compartment increase and the lack of increase in the internal capsule white matter volume, in turn, may imply a lesser involvement of connections between cortex and subcortical structures.

Our data suggest that this increased white matter volume may derive more from alterations intrinsic to white matter than from an increased number of neurons leading to more myelinated axons. First, overall cortical volume in these brains is not increased but relatively smaller in both DLD and autism[11,15]; neuronal number increase thus is unlikely without increased packing density or other cytoarchitectonic alterations. (On this point the limited existing literature is equivocal: altered "minicolumns"[35] might indicate increased neuronal number, whereas unchanged *N*-acetylaspartate by spectroscopy,[36] along with our lack of cortical volume increase,[11] suggests the opposite.) Beyond this, ipsilateral corticocortical or associational fibers, as well as the bulk of commissural and callosal axons, arise predominantly from neurons in layer III of the neocortex.[37,38] In contrast, internal capsule and other corticosubcortial projection fibers mostly arise from cell bodies in layers

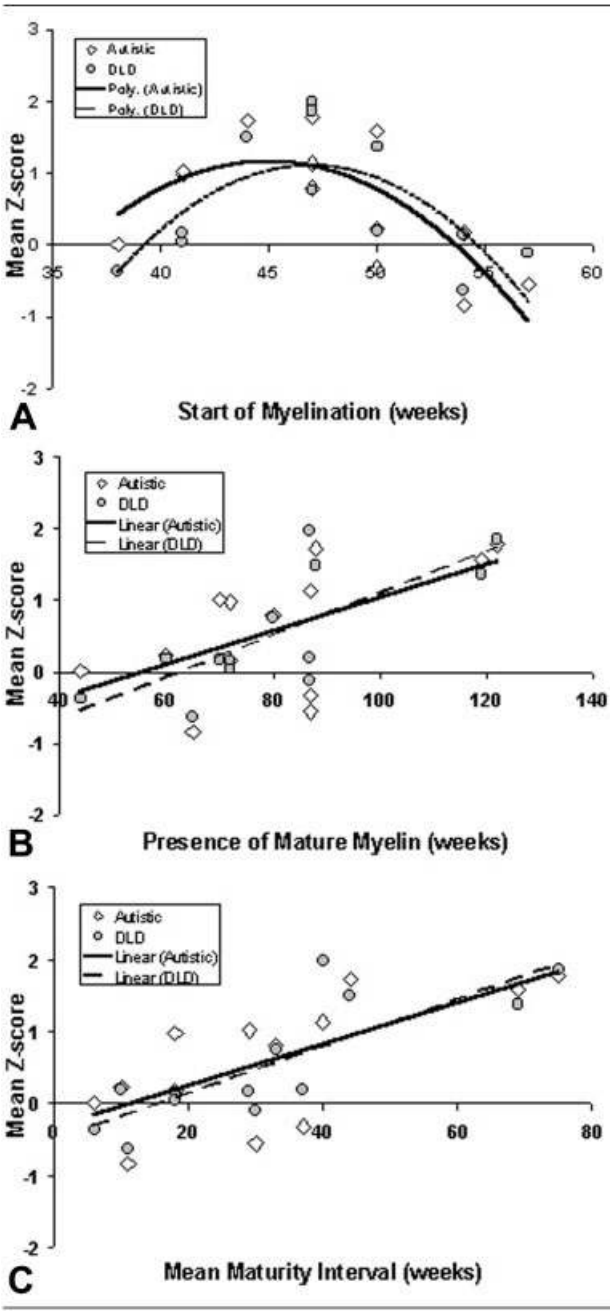

Fig 5. Volume differences between each study group and controls are expressed as Z-scores standardized to the control volumes. They are graphed as a function of the (A) postconceptional week of myelination onset *(ie, start of* solid bars *in Fig 2), (B) postconceptional week of* myelination maturity *(ie, end of* solid bars *in Fig 2), and (C) duration (in weeks) of the* myelination interval *(ie, length of* bars *in Fig 2). Poly. = Polynomial (nonlinear best fit line); DLD = developmental language disorder.*

V and VI. With a uniform increase in neuronal number in any of these layers, we would not expect the dissociation we see between enlarged radiate compartment white matter and unaltered volumes of both corpus callosum and internal capsule. However, although volumetric data can raise these issues, resolution will require more microscopic investigation.

Functional Implications

Overall, although there are several differences between autism and DLD brains regarding the distribution of white matter enlargement in the radiate compartment, they correlate only loosely with either the phenotypic distinctiveness of each disorder or the phenotypic overlaps between them. For example, frontal and prefrontal white matter enlargement differ between the disorders in degree but not in kind, whereas executive function disorders associated with this area have been found in autism but not in DLD.[39] Thus, a localization approach yields functional implications that are suggestive but rather equivocal.

The anatomical distribution of white matter enlargement discerned by our white matter parcellation appears to be more related to a temporally modulated process than to a circuit or distributed system-specific process. Certainly components of multiple circuits will be impacted by alterations in the radiate compartment of white matter. However, the underlying biology leading to this increase may implicate these circuits only incidentally, as opposed to targeting them in a primary fashion. It thus should not be surprising that lobar-based attempts at differential clinical-pathological correlation should yield ambiguous results.

Nonmodular approaches to clinical-pathological correlation may be more useful for making sense of the functional implications of this widespread radiate white matter enlargement. Abnormal white matter potentially may contribute to proposed underlying pervasive core processing deficits, such as impaired complex information processing[40] or weak central coherence[41] in autism, and impaired multimodal or rapid processing in DLD,[42] that some have suggested are at the root of the behavioral features of these disorders. The language functions impaired in both autism and DLD, and the behavior and communication impairments in autism, are all higher level functions that are likely to involve substantial cross-modal information processing[40,43] and thus associational cross-talk; they thus may be particularly vulnerable to disturbed connectivity.[44] Because the widely distributed white matter enlargement in these autism and DLD brains may have significant impact on connectivity, it thus may plausibly result in functional deficits that appear modular.[44] At the same time, a widespread abnormality in white matter also might underlie many of the more subtle or variable secondary features encountered in these disorders, that include a range of neurological and processing impairments.[45]

A quite different possibility is that white matter enlargement is not a cause of functional impairment, but an effect. Because oligodendrocytes are responsive to neuronal activity,[46] myelin increase could be a secondary consequence of increased physiological "noise." This could be a nonspecific response to a primary phenomenon of disordered brain activity that reflects a temporally progressive, molecularly based disruption of microcircuitry. That the magnitude of anomaly is greater in autism than in DLD may follow from differences in regional expression and magnitude of circuitry dysfunction in the two disorders.

Conclusion

Clearly, our DLD and high-functioning autism samples show much similarity in distribution of white matter enlargement. The strong similarities suggest a substantial overlap of risk factors[47] and raise the possibility that these disorders may be on a spectrum rather than being clearly distinct from one another.[48] Certainly, there are several notable differences between the autism and DLD white matter volume profiles. However, the anatomical differences we report here may not be centrally distinguishing in themselves but may only reflect varying modulations of a similar underlying process. These differences, whatever their significance, should not overshadow the striking similarities.

The radiate white matter enlargement that we have found in both autism and DLD has important implications for pathogenesis and developmental timing. Our evidence strongly suggests that this enlargement develops postnatally and is caused by a temporally modulated process. The distribution of volume changes is not consistent with an increased number of cortical neurons driving an increase in axon number but instead suggests a process that alters some nonaxonal component of white matter, possibly myelin. Testing of these volumetrically derived hypotheses through further characterization of this white matter alteration should help guide the search for genetic or environmental factors that might perturb white matter development in this fashion. Knowledge thus gained may bring us closer to treatments to halt this perturbation or identification of triggers whose avoidance might prevent it.

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