Large Brains in Autism: The Challenge of Pervasive Abnormality

MARTHA R. HERBERT
Pediatric Neurology, Center for Morphometric Analysis
Massachusetts General Hospital

The most replicated finding in autism neuroanatomy—a tendency to unusually large brains—has seemed paradoxical in relation to the specificity of the abnormalities in three behavioral domains that define autism. We now know a range of things about this phenomenon, including that brains in autism have a growth spurt shortly after birth and then slow in growth a few short years afterward, that only younger but not older brains are larger in autism than in controls, that white matter contributes disproportionately to this volume increase and in a nonuniform pattern suggesting postnatal pathology, that functional connectivity among regions of autistic brains is diminished, and that neuroinflammation (including microgliosis and astrogliosis) appears to be present in autistic brain tissue from childhood through adulthood. Alongside these pervasive brain tissue and functional abnormalities, there have arisen theories of pervasive or widespread neural information processing or signal coordination abnormalities (such as weak central coherence, impaired complex processing, and underconnectivity), which are argued to underlie the specific observable behavioral features of autism. This convergence of findings and models suggests that a systems- and chronic disease–based reformulation of function and pathophysiology in autism needs to be considered, and it opens the possibility for new treatment targets. NEUROSCIENTIST 11(5):417–440; 2005. DOI: 10.1177/0091270005278866

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Autism is a developmental disorder defined behaviorally by a triad of abnormalities involving language, social interaction, and a marked lack of flexibility that may include repetitive or ritualistic behaviors (American Psychiatric Association, 1994); full criteria must be met by the age of three. The behavioral features of autism appear to be continuously distributed, and autism is part of a spectrum that also includes more mildly affected individuals (Dawson and others 2002).

Given that the atypical behaviors defining autism appear specifically characterizable, there has naturally been the expectation that we will find anatomical correlates for each feature of the behavioral phenotype. Indeed, there are findings in the limbic system and cerebellum (parts of the brain subserving functions that include some impaired in autism) that have been common (Cody and others 2002), yet they are troublingly not consistently encountered. Instead, the most replicated finding in autism, and one that has been found in multiple reliably characterized cohorts and artifact-free samples, has been that the brains are on average unusually large. This finding has had a paradoxical impact. On one hand, the consistency of an anatomical measure was an encouraging sign of convergence upon unraveling the neurobiology of this disorder. On the other hand, large brains did not make sense in terms of neural systems models of autism or brain-behavior correlations. How would such a generalized phenomenon relate to a disorder characterized by three specific classes of atypical behaviors? This conundrum has been sitting in the center of the autism field almost like a zen koan, awaiting a mental frame shift that would allow its obscure significance to become clear.

In the past few years, a series of discoveries about the autistic brain are appearing to converge toward a model that integrates biological, processing, and behavioral levels in autism. These discoveries potentially shed light on large brains regarding both underlying mechanisms and functional consequences. Moreover, these findings point toward a disease model that departs from earlier formulations of autism in having several new levels of potential treatment implications. The recent findings prominently include identification of pervasive volume scaling alterations, widespread reductions in connectivity and perfusion, and neuroinflammation and microgliosis that had previously been unappreciated. Identification of these features of the autistic brain for the most part was driven by investigation of tissue and processing in autism and not by seeking specific correlates for specific behaviors, at the level of either brain or gene. Nevertheless, these features hold implications for

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Address correspondence to: Martha R. Herbert, Pediatric Neurology, Center for Morphometric Analysis, Massachusetts General Hospital, Harvard Medical School, 149 13th Street, Room 6012, Charlestown, MA 02129 (e-mail: mherbert1@partners.org).

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underlying gene and gene-environment mechanisms as well as for understanding the resulting behavioral and medical abnormalities. Alongside these empirical findings, models have emerged of more generalized deficits or disturbances in autism, at the level of processing (weak central coherence [Hill and Frith 2003], impaired complex processing [Minshew and others 1997], network abnormalities [McClelland 2000; Brock and others 2002; Cohen in press], disordered information processing [Belmonte and others 2004]) and at the neurochemical level (models of increased excitation-inhibition ratios [Rubenstein and Merzenich 2003]), that have been argued to underlie the specific behaviors we observe.

With these new findings and models, the phenomenon of large brains in autism has been joined by a set of other pervasive abnormalities. On one hand, this means there are yet more widespread phenomena that somehow paradoxically have to make sense in relation to a disorder that has been defined as a set of specific behaviors. But on the other hand, these pervasive findings flesh out details and suggest linkages between functional, macroanatomical, and pathophysiological levels. They do not displace prior regional findings, but on the other hand, they provide a framework within which previous observations can be viewed in a fresh light, as we will see below.

To date, investigations of pervasive phenomena in autism have been weighted toward gathering various classes of data, particularly in the domain of brain size measurement (largely MRI volumetrics and head circumference studies), that increase the level of nuance at which we are able to describe the regionally differentiated macroscopic neuroanatomy and the temporal trajectory of autistic brain enlargement, as will be described below. The more recent developments in the field suggest that further methodologies will need to be used for characterizing the hitherto less well-studied dimensions of brain structure and function—such as tissue characterization, neuroimmunological and neurometabolic measures, and functional connectivity—that have taken on new relevance more recently.

Brains Are on Average Larger

Although there is a strong trend toward bigger brains in autism, this phenomenon by no means constitutes a biomarker for the disorder. Frank macrocephaly is defined as a head circumference greater than the 97th percentile, which by definition means that it is found in 3% of the population. Given a U.S. population of approximately 300 million, certainly the vast majority of the 9 million individuals with macrocephaly are not autistic. What is more interesting is that among autistic individuals, the percentage with macrocephaly is not 3% but more in the range of 20% (Steg and Rapoport 1975; Walker 1977; Bailey and others 1993; Rapin 1996; Lainhart and others 1997; Stevenson and others 1997; Fombonne and others 1999; Aylward and others 2002; Deutsch and Joseph 2003; Dementieva and others 2005), with an overall upward shift in head circumference distribution even for those who do not meet criteria for macrocephaly (Gillber and de Souza 2002; Deutsch and Joseph 2003; Dementieva and others 2005). Thus, although not a biomarker, macrocephaly appears to be a phenomenon, or an endophenotype, that provocatively suggests the existence of a relevant underlying pathophysiology. Yet even here, the pathophysiology leading to macrocephaly in autistic individuals does not seem in itself sufficient for autism because macrocephaly is also common in their first-degree (and unaffected) relatives (Fidler and others 2000). Macrocephaly also does not appear to be specific to autism, also being found in pervasive developmental disorder (Woodhouse and others 1996), attention deficit hyperactivity disorder (Ghaziuddin and others 1999), and developmental language disorder (Herbert, Ziegler, Makris, and others 2003). Nor is it specific for any one autism phenotypic subgroup (Miles and others 2000), although individuals with Asperger syndrome were found to have larger mean head circumferences than those with autism (Gillberg and de Souza 2002).

Over the past decade and a half, volumetric neuroimaging has been contributing considerably more detail to the characterization of increased brain volume in autism (Table 1). Large brain volume was early reported by Filipek and others (1992) in a sample in which high-functioning autistic school-age children had larger brain volumes than did lower functioning (nonverbal IQ <80) children and controls. Piven and others (1995) studied 20 male autistic subjects who were found to have larger brains due to enlarged tissue and lateral ventricle volume, with a follow-up study showing the enlargement in males but not in females and in temporal, parietal, and occipital but not in frontal lobes (Piven and others 1996). Enlargement of gray and white matter in the cerebrum and cerebellum was found in 2- to 3-year-olds by Courchesne and others (2001), whereas cerebral but not cerebellar enlargement was found in 3- to 4-year-olds by Sparks and others (2002). Brain volume was larger than controls for autistic subjects younger than 12 years (Aylward and others 2002). For school-age boys with high-functioning autism, brain enlargement bordered on significance (Herbert, Ziegler, Deutsch, and others 2003). In a study comparing high-functioning and low-functioning autism and Asperger syndrome with controls in mid-childhood through adolescence, cerebral gray matter but not white matter enlargement was found (Lotspeich and others 2004).

Brain Growth Trajectories Are Atypical

Some of the earliest observations of increased brain size were in postmortem brain weight measures (Bauman and Kemper 1985). Although neuropathological investigations are complicated by limited control over subject ascertainment, comorbidities, conditions of death, and postmortem interval and may involve confounds such as edema that may affect brain weight, these measures are nevertheless of interest. Postmortem studies have not

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Table 1. Studies of Brain Size in Autism

Author(s) (Year)	Question	*N*	Methods	Key Measures	Findings	Interpretation
Davidovitch (1996)	Is there a correlation between large HC and autism?	148 autistic	HC measured and divided into two groups: above and below and autism? 98th percentile for HC.	HC	27/148 (18.2%) were at or above the 98th percentile; height and weights were also significantly greater in this group.	There may be a correlation between large HC and autism.
Woodhouse and others (1996)	Is macrocephaly a phenotype of autism?	89 autistic	HC measured from 1 year's worth of new cases in autism and PDDs.	HC	No difference between PDD and autism cases for macrocephaly. For PDD group, 29.7% had macrocephaly; 48.7% had head circumference greater than 90th percentile.	Both autism and general PDDs are associated with macrocephaly; therefore, macrocephaly may be an indicator of heterogeneity or an indicator of disease severity. Macrocephaly may be a distinct subgroup of autism.
Lainhart and others (1997)	What is the frequency and onset of macrocephaly in autism and how is it related to clinical features?	91 autistic; 70 males, 21 females; age range, 3–38 y; mean age, 13.8 y; no controls	HC measured at birth and throughout the life cycle in children and adults with autism.	HC	14% of subjects had macrocephaly; 11% male, 24% female. Mostly not present at birth but began during early childhood as a result of increased rate of head growth. Core features of autism tended to be less severe in autistic subjects with relatively large head sizes for their age and gender. Neither macrocephaly nor HC were associated with nonverbal IQ, verbal status, seizure disorder, neurological soft signs, or minor physical abnormalities.	Macrocephaly does not characterize a homogeneous subgroup of autistic individuals according to clinical features and may change throughout the life cycle.
Ghaziuddin and others (1999)	Is megalencephaly specific to autism?	20 autistic; 20 males; mean age, 10.9 y (included autism and general PDD); 20 controls (ADHD)	Measure HC.	HC	4 subjects (all purely autistic) and 5 controls had megalencephaly (2 SD > mean). The 4 subjects with autism also had hyperactivity and impulsivity.	Megalencephaly may not be specific to autism. These findings suggest that both autism and ADHD are associated with megalencephaly.

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Author(s) (Year)	Question	*N*	Methods	Key Measures	Findings	Interpretation
Fombonne and others (1999)	What is the rate of macrocephaly in autism?	126 autistic; age range, 2–16 y, mean age, 7.9 y	Measure HC.	HC	Macrocephaly (HC > 97th percentile) in 16.7% of autistic population. Associated with increased age but not other variables such as gender or severity.	Results suggest an increased rate of macrocephaly in autism.
Fidler and others (2000)	Is the prevalence of macrocephaly greater in autism than in the general population?	41 autistic; mean age, 13.5 y; 133 first-degree relatives; 21 controls	Familiality of HC assessed from measurements of first-degree relatives.	HC	Rates of macrocephaly were significantly higher in probands with autism (12.2%) and their first-degree relatives (15.5%) than in published normative sample. HC and extreme macrocephaly found to be heritable (H2 = 0.47).	Macrocephaly may be a familial risk factor in the pathogenesis of autism due to the increased prevalence of macrocephaly in relatives of children with autism compared with control children.
Miles and others (2000)	Is head size a phenotypic variable that will define genetically distinct autism subgroups?	137 autistic; 115 males, 22 females; age range, 1–41.2 y; mean age, 9.4 y	Measure HC.	HC	The HC in the autism group was significantly larger than in the normal population. No differences in age, gender, or other related variables. Within subgroups (phenotypic status, type of onset, seizure history, IQ), all had significantly higher than normal mean HC measurement. Macrocephaly is familial, with 45% in autism group having at least one macrocephalic parent.	Because HC increased significantly even within subgroups, macrocephaly is an independent clinical trait in autism.
Gillberg and de Souza (2002)	Is macrocephaly associated with high-functioning autism, and is it seen in similar disorders such as ASP and ADHD?	50 autistic: 45 males, 5 females; age range, 1.3–13.7 y; mean age, 8.3 y; 100 controls (50 ASP, 50 ADHD): 90 males, 10 females; age range,	HC measured at two time points: at birth and at or after 16 mo of age.	HC	Autistic and control groups had mean HC at birth larger than normal values. Asperger group had greater HC than autistic group did. Autism group at birth had 4/42 macrocephalic at birth ($P < 0.01$) and 4/42 (ns) after 16 mo of age. All groups also had mean HC greater than age and gender norms when examined after 16 mo of age. At 16 mo of age, the Asperger group was	Macrocephaly appears to be more common in higher functioning levels of autism such as Asperger syndrome and is not as common in "classic" lower functioning autism classes. At birth, the mean HC was high in all groups but lower at or after 16 mo. In addition, "new" cases emerged at

		1.5–16 y; mean age, 8.6 y			significantly greater than the ADHD group but not the autism group.	the later time points that were not present at birth. This study suggests that macrocephaly might not be as clinically useful as previously thought.
Deutsch and Joseph (2003)	What are the frequency and cognitive correlates of enlarged head circumference?	63 autistic; 54 males 9 females; age range, 4–14 y	HC measured and studied with several variables: verbal and nonverbal cognitive ability, language level, executive function, and symptom severity.	HC	Macrocephaly occurred in autism subset at significantly higher frequency than in normal reference sample. HC not correlated to variables studied but correlated with discrepancies between verbal or nonverbal IQ scores, with nonverbal IQ > verbal IQ, independent of the absolute level of verbal ability.	Convergence of physical and cognitive features may indicate an etiologically significant subtype of autism.
Courchesne and others (2003)	Does pathological brain overgrowth precede the first clinical signs of autism? Is the rate of overgrowth during the first year related to neuroanatomical and clinical outcome in early childhood?	48 autistic: age range, 2–5 y; 51 controls: 26 males, 25 females	HC, body length, and BW measurements during first year obtained from medical records in children who had participated in previous MRI studies.	HC	Birth HC in autistic infants was significantly smaller ($z = -0.66$, $P < .001$). After birth, HC increased 1.67 SDs, and mean HC was 84% at 6–14 mo. Birth HC related to CRBLR-GMV at 2–5 y, although the excessive increase in HC between birth and 6–14 mo was related to increased CCTXV at 2–5 y. Compared to infants with PDD-NOS, every subject in the autism group had a greater increase in HC between birth and 6–14 mo (respectively, (mean [SD], 0.58 [0.35] vs. 2.19 [0.98]). Of autism group, 59% had accelerated growth trajectories (>2.0 SD) in a longitudinal study compared to 6% in the healthy group from birth to 6–14 mo.	Two phases of brain growth abnormalities appear to precede the clinical emergence of autism: 1) a reduced head size at birth then 2) a sudden and excessive increase in head size between 1–2 mo and 6–14 mo. This abnormally accelerated rate of growth may represent a clinically sound, early risk sign for autism.

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Author(s) (Year)	Question	*N*	Methods	Key Measures	Findings	Interpretation
Dementieva and others (2005)	Is abnormal acceleration in head growth during early development, rather than macrocephaly, associated with autism risk?	251 autistic; 183 males, 68 females; M:F = 2.7:1; mean age, 8.15 y, SD = 4.43 y; longitudinal = 79	HC measured in 82 multiplex and 113 sporadic families with autism, with longitudinal (records for more than 2 HC measurements) mean for 79. Abnormal acceleration in head growth definition: >25th percentile HC growth between two consecutive measurements.	HC	19% of the original 251 had macrocephaly, 66% males, 34% females. From the longitudinal group, 35% had abnormal increases in HC. Those with abnormal growth in early childhood had higher levels of adaptive functioning and less social impairment. 37/79 had serial measurements starting at birth, 24/39 (65%) showed abnormal acceleration of head growth. Found a significant association between HC percentile and age at the time of head measurement, $F(18, 145) = 4.06$, $P < 0.0001$. Further adjustments showed that the significant (adjusted P value = 0.005) difference in the least squared means occurred between the first (0–1 mo) and second (1–12 mo) age classes and none between other age classes. 42/79 had HC measurements in the first time period (0–1 mo) and showed that the mean HC % = 48th percentile, SD = 29, with 2/79 having macrocephaly, with both having a family history of macrocephaly. 17/42 had measurements in the second time period (1–2 mo) = 79th percentile, SD = 20, showing abnormal head growth acceleration. 17/17 had measurements in the third time period (2–6 mo) = 77th percentile, SD = 25.7, 3 macrocephalic.	Study supports presence of abnormal acceleration of head growth during months 1 and 2 of life in a subgroup of individuals with autism. Findings show that macrocephaly appears to be of secondary importance in relation to abnormal acceleration in head growth at the earliest stages of postnatal development. May be a risk factor associated with autism.

Piven and others (1995)	What is the volume of the brain in subjects with autism and how is it different than in normal individuals?	22 autistic males; 20 male controls	SMRI: TBV, total brain tissue volume, TTLVEN.	SMRI	Autistic subjects had significantly greater TBV, total brain tissue volume measurements, and TTLVEN.	Findings suggested that the brain enlargement was a result of greater BTV and greater TTLVEN.
Piven and others (1996)	Is increased brain volume in autism the result of general or regional brain size differences, and is there an effect of gender on brain size and the pattern of enlargement?	35 autistic: 26 males, 9 females; 36 controls	SMRI, TBV, and CCTX lobe volume, controlled for height and nonverbal IQ.	SMRI	Significant diagnosis × gender effect, $F = 7.4$, $P = .009$, for TBV. An analysis of lobe sizes showed significant enlargement in autistic subjects in the temporal, parietal, and occipital lobes but not the frontal lobes.	Findings support brain size increase in autism; differences between normal and autistic brains appears to be the result of a pattern of enlargement with increases in the size of specific cortical lobes, not a generalized phenomenon.
Courchesne and others (2001)	What are the developmental abnormalities in the neuroanatomical structure and volume of the CCTX and CRBLM in subjects with autism?	60 autistic males: age range, 2–16 y; 52 male controls: age range, 2–16 y	SMRI: TBV, CCTX, CRBLM, and HC.	HC and SMRI	14/15 normal HC at birth. By 2–4 y of age, 90% had TBV larger than normal average, and 37% met criteria for developmental macroencephaly, Autistic 2- to 3-year-olds had 18% more CCTX WM, 39% more CRBLR WM, and 12% more CCTX GM than controls did, whereas older autistic children and adolescents did not have enlarged gray and white matter volumes. In CRBLM, autistic boys had less gray matter decreased ratio of gray-white matter and smaller vermis lobules VI-VII than controls did.	Abnormal regulation of brain growth in autism consists of two phases: abnormally early over growth followed by a later phase of abnormally slowed growth.

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Author(s) (Year)	Question	*N*	Methods	Key Measures	Findings	Interpretation
Hadan and others (2001)	Is TBV increased in non–mentally retarded individuals with autism, as has been reported in previous studies of LFA individuals?	16 autistic males: mean age, 22.2 y; 19 male controls: mean age, 22.2 y	SMRI: TBV, IC, vent.	SMRI	Increased TBV and third vent after controlling for intracranial volume.	The findings of increased brain volume in non–mentally retarded individuals is consistent with previous reports of lower functioning autism, providing further support for the significant of enlarged brain volume.
Alyward and others (2002)	Does brain volume differ between individuals with autism and control subjects (BV), and are these differences affected by age?	67 autistic: 58 males; mean age, 18.8 y; 83 controls: 76 males; mean age, 18.9 y	SMRI: TBV and HC.	HC and SMRI	Greater TBV seen only in cases younger than 13 y. No significance detected when they took the TBV of group as a whole, regardless of age. Increased HC in all autistic subjects regardless of age.	Abnormal brain development and growth patterns. Accelerated early growth and enlarged brain and HC followed by a slowed growth in adulthood that causes brain to appear normal, but in fact, it decreases from its initial enlarged state.
Sparks and others (2002)	What are the neuroanatomical abnormalities associated with autism in young children?	45 autistic: 38 males, 7 females; age range, 3–4 y, mean age, 47.4 mo; 26 controls: DD 14	SMRI: cerebrum, CRBLM, hippocampus, amygdala.	SMRI	Autism group had significantly increased cerebral volumes. Relative increases in volume were also seen in the CRBLM and bilaterally in the amygdala and hippocampus, though these increases were proportional to the overall increase in cerebral volume. Similar findings seen between genders.	The structural abnormalities suggest that the abnormal brain developmental probems seen in autism are lmanifested during early childhood.
Herbert and others (2003a)	What is the comprehensive morphometric profile of large brain structures in autism?	17 autistic: age range, 7–11 y; 15 controls: age range, 7–11 y	SMRI: TBV, CCTX, CWM, CRBLM, caud, lent, thalamus/hypothalamus, HPAM, BS. Gray-white segmentation of major brain regions. Volumes, adjusted volumes (adjustment for total brain volume), and factor analysis.	SMRI	TBV close to significantly larger. Three factors: cerebral white matter both absolutely and relatively larger, cerebral cortex and hippocampus-amygdala absolutely same but proportionately smaller, remainder absolutely same or slightly larger but proportionately no different than controls.	Large brain size is constituted by tissue changes that affect brain structures in a nonuniform fashion with white matter increases predominantly driving volume increase in this age group.

Lotspeich and others (2004)	Are there neuroanatomical differences between low-functioning and high-functioning autism (LFA, HFA) and ASP, and what are these specifically?	LFA 13, HFA 18, ASP 21, controls 21; all males, 7.8–17.9 y	SMRI: total, white, and gray matter for cerebrum and CRBLM.	SMRI	Intersite differences seen for the age, IQ, and CRBLM measure of the subject. CGM-V was enlarged in HFA ($P = 0.009$) and LFA ($P = 0.04$) compared to controls, in ASP intermediate between HFA and controls but not significant. Negative correlation between CGM-V and performance IQ within HFA but not ASP. Positive correlation between CWM-V and performance IQ within ASP but not HFA.	CGM volumes suggest that ASP is on the mild end of the autism spectrum and is different from HFA. Age, IQ, and CRBLM measures are relevant.
Williams and others (1980)	Can the neuropathologic abnormalities in the autistic brain provide clues for the etiology of autism?	4 autistic; 3 males; age range, 4–33 y; mean age, 19.5 y	Postmortem brains weighed and sectioned for neuropathologic examination.	TBW	At the time of autopsy, brain weights were within 2 SDs of normal for the appropriate age. Neuropathologic examination revealed nerve cell loss and gliosis in atrophic orbitofrontal and temporal regions. Smaller neurons were observed in the CA4 region. Decreased Punkinje cell packing density in the 4-year-old case.	There were not consistent findings between cases to provide clues as to the cause of the pathoanatomical result. More studies are needed.
Kemper and Bauman (1998)	What are the neuropathological abnormalities in the autistic brain?	19 autistic	Brain weight obtained. Then used gapless sections of the whole brain to compare an autistic adult with an age- and gender-matched control.	TBW	8/11 brains <12 y of age showed a significant increase in weight as compared with controls. 6/8 > 18 y of age had brain weight less than expected, but the differences did not reach statistical significance. Cells in several regions were larger and more abundant in younger brains but smaller and fewer in older brains.	There is an age-related volume change, and cellular changes appear to suggest an ongoing process.
Bailey and others (1993)	What is the underlying pathology to the genetic basis of autism?	4 autistic; age range, 4–27 y; mean age, 19.25 y	Measure total brain weight of postmortem brains.	TBW	All significantly greater than normal range for brain weight for age bracket. Average brain weight = 1.6 kg, normal range (average for 2 age groups) = 1.32–1.42 kg.	Some cases of autism are associated with abnormal brain development.

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Table 1. (continued)

Author(s) (Year)	Question	*N*	Methods	Key Measures	Findings	Interpretation
Guerin and others (1996)	What causes the neuroanatomical abnormalities seen in autism?	1 autistic; 1 female; age, 16 y	Direct microscopic observation of the whole brain.	TBW	Low brain weight, a thin CC, and increased size of ventricles was found. No microscopic abnormalities were found.	This case does not lend any insight into the etiological origin of the neuro-anatomical abnormalities found.
Bailey and others (1998)	Are neuropathological abnormalities (Nab) more extensive than previously supposed? Evaluate the previous observations.	6 autistic: 6 males; age range, 4–27 y; mean age, 20 y; 7 controls: 5 males, 2 females; age range, 4–27 y; mean age, 25 y	Brains weighed intact, then BS and CRBLM separated and weighed. One CRBLM hemisphere sliced, fixed, stained, embedded. CCTX, hippocampus, and CRBLM compared histologically vs. matched controls. Immunohistochemistry. Morphometry: neuronal counts from parts of superior frontal gyrus ACC; CA1, 2, 4 of hippocampus; Purkinje cells.	TBW	4/6 brains megalencephalic. Pathological, developmental abnormalities found in CCTX: 4/6 cortical dysgenesis and 5/6 abnormalities in the underlying white matter: increased number of white matter neurons and some gliosis; BS: 4/6 olivary dysplasia, neuronal ectopia, and others. CRBLM: 5/6 decreased Purkinje cells, 3/6 increases in GFAP, and 4/6 Bergmann glia (2, 3, 5, 6).	Findings do not support previous claims of localized neurodevelopmental abnormalities, but increased brain size and other findings point to involvement of CCTX in autism.
Courchesne and others (1999)	Is megalencephaly common in autism?	21 autistic, 6 controls	TBW postmortem of 16 previously published and 5 new cases compared with normal brain weights from 6 autopsy studies.	TBW	17/21 cases have normal BW, 3 megalencephalic, 1 microencephalic.	Brain weight is usually normal in postmortem cases of autism, although there are occasional cases of megalencephaly and rarely microencephaly.

HC = head circumference; PDD = pervasive developmental disorder; ADHD = attention deficit hyperactivity disorder; ASP = Asperger syndrome; ns = nonsignificant; BW = brain weight; CRBLR-GMV = cerebellar gray matter volume; CCTXV = cerebral cortex volume; PDD-NOS = pervasive developmental disorder not otherwise specified; SMRI = structural MRI; TBV = total brain volume; TTLVEN = total ventricles; BTV = bilateral total ventricles; CCTX = cerebral cortex; CRBLM = cerebellum; LFA = low-functioning autism; IC = internal capsule; vent = ventricle; BV = bilateral ventricles; DD = developmentally delayed; CWM = cerebral white matter; HPAM = hippocampus-amygdala; BS = brain stem; HFA = high-functioning autism; CGM-V = cerebral gray matter volume; TBW = total brain weight; CC = corpus callosum; ACC = anterior cingulate cortex; GFAP = glial fibrillary acidic protein.

consistently reported total brain weight, but when reported, it tended to be markedly above average, particularly in younger subjects. The early sample of Williams and others (1980) included 4 brains all with brain weights within 2 standard deviations of the mean for age, but 3 of the subjects were older than 12 years at the time of death. Kemper and Bauman (1998) reported that of 19 brains for which weight was available, 8 of the 11 brains of subjects who were younger than 12 years were increased compared to controls, whereas 6 of 8 brains from individuals older than 18 years weighed less than expected. Of the 6 brains in the Bailey and others (1998) sample, 4 (including a 4-year-old and 3 individuals in their 20s) were frankly above the normal range derived from Dekaban and Sadowsky (1978), whereas the remaining 2 (also in their 20s) were near the upper limit of that range (Bailey and others 1998). Courchesne and others (1999) observed that a problematic error term in the Dekaban and Sadowsky (1978) data complicates its use as a source of norms for these comparisons.

Larger brains in younger but not in older subjects has also been found in brain imaging. Aylward and others (2002) measured both head circumference and brain volume and found that both measures were larger in autistic children younger than 12, whereas only head circumference was larger in older autistic individuals, suggesting an early rapid brain growth with the volume initially achieved not being maintained through the life course. Brain volume was enlarged in 2- to 4-year-olds but not in teenagers studied by Courchesne and others (2001). The failure of Lotspeich and others (2004) to replicate many prior findings of brain enlargement may be due to the ages of their subject pool straddling a wide range, from 7.8 to 18.9 years, an interval that overlaps with both younger subjects in whom brain enlargement has been discerned and an older group in whom brain enlargement has not been found. Of note, volumetric studies to date have been cross-sectional; at the current time, the longitudinal study of autism, which would generate more meaningful data, is just getting under way.

It is of particular interest to study brain growth trajectories in autism from birth (Redcay and Courchesne 2005). To date, several retrospective head circumference studies have been performed. A small minority of children in these studies manifested macrocephaly at birth (Mason-Brothers and others 1990; Lainhart and others 1997; Gillberg and de Souza 2002; Courchesne and others 2003), but for the most part, across studies, autistic children did not exceed the 97th percentile at birth (Lainhart and others 1997; Stevenson and others 1997; Hultman and others 2002; Courchesne and others 2003). Lainhart and others (1997) reported that head circumference increased toward macrocephaly in early to mid-childhood, whereas Courchesne and others (2003) found that the bulk of the unusual growth trajectory—an increase of 2 standard deviations—was accomplished by 14 months of age, with a marked slowing of growth rate thereafter. Dementieva and others (2005), with a much larger sample, showed, as did Courchesne and others' (2003) study, an abnormal brain size increase beginning in the first 2 months of life but continuing for several years (Fig. 1), demonstrating that many individuals who did not become macrocephalic nevertheless manifested this abnormal early postnatal burst of brain growth (Dementieva and others 2005). In Courchesne and others' (2003) neuroimaging samples, in which the age range of subjects cut through much of childhood, the early rapid brain growth was followed by a much slower rate of growth relative to controls in subsequent years of childhood (Carper and others 2002).

The extremely desirable information about aberrations in brain development during the period of most rapid brain growth (and during the period when the brain enlarges atypically) that could be derived from prospective brain imaging data is difficult to acquire. Given the lack of biomarkers that would identify autistic individuals at birth or in early infancy, and given that the diagnosis is made on the basis of behaviors such as language and socialization that are not well-defined for the first few years, the available alternative is to study infants and young toddlers at risk for autism due to the diagnosis of an older sibling in the family. But serious ethical constraints apply to the study of undiagnosed individuals this young, including the inappropriateness of using sedation agents that complicated the achievement of stillness requisite for MRI scanning; this leaves the option of patiently waiting and then maintaining spontaneous sleep. The first such study reports that in two year olds with autism there is generalized enlargement of gray and white matter cerebral but not cerebellar volumes, that may have its onset post-natally in the latter part of the first year of life (Hazlett, Poe, Gerig and others forthcoming).

White Matter Contributes Disproportionately to Brain Volume Enlargement

Several studies found that increased brain volume in young autistic individuals appears to be largely driven by an increase in white matter, although in a diminishing fashion as development progresses and overall brain enlargement relative to controls disappears. In Courchesne and others' (2001) study of 2- to 16-year-olds, white matter enlargement (18% more cerebral and 38% more cerebellar white matter) was found in 2- to 3-year-old autistic children accompanied by cerebral cortex enlargement, whereas 12-to 16-year-old autistic children in this study had less white matter than controls did (Courchesne and others 2001). In a comprehensive volumetric profile of high-functioning autistic boys intermediate in age between Courchesne and others' younger and older subjects, Herbert, Ziegler, Deutsch, and others (2003) reported that white matter was 15% larger in 6- to 12-year-old autistic boys than in age-matched controls, making up less than a third of cerebral volume but accounting for 65% of the volume increase in autism over controls (Fig. 2); while at the same time, the cerebral cortex and hippocampus-amygdala were propor-

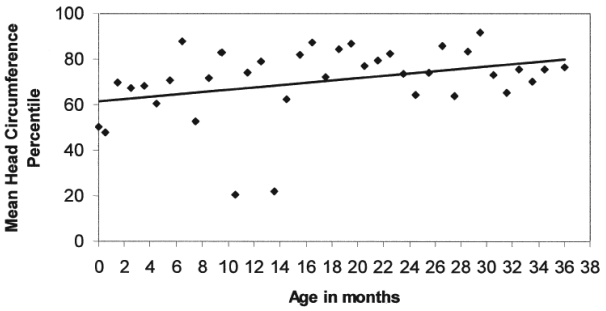

Fig. 1. In a sample of autistic individuals, Dementieva and others (2005) showed a continuous increase in head circumference percentile from birth through 3 years, with a linear regression between mean head circumference percentile and age, by month of age from 0 through 36 months. (There was only one child between 10 and 11 months and one between 13 and 14 months.)

tionately smaller than in controls and the remaining major brain structures were absolutely larger but not larger once overall size increase was taken into account (Herbert and others 2003a; Fig. 3). In older autistic individuals, voxel-based methods have shown less white matter concentration (a different measure than volume) than in age-matched controls (Chung and others 2004; Waiter and others 2005).

Regionalization of White Matter Volume Increase

Herbert's group performed a further analysis to characterize regional biases in this white matter volume increase, using a method of topographical white matter parcellation based on the neuroanatomy of white matter tracts (Makris and others 1999; Meyer and others 1999). The results were that the volume increase is confined to the radiate zone, that is, the subcortical white matter primarily composed of corona radiata and U-fibers but also including the origins and terminations of projection and sensory fibers. In this study, the deeper white matter, including major sagittal tracts, internal capsule, and corpus callosum, showed no volume increase over controls (Herbert and others 2004). The frontal lobe white matter showed the greatest enlargement over controls (27%), with frontal lobe predominance also previously reported by Carper and others (2002) and with prefrontal white matter even more strongly affected (36% larger than controls; Herbert and others 2004; Fig. 4). Herbert and others (2004) reported a further regression analysis that combined temporal and spatial considerations, addressing regional white matter volumes in relation to the timetable of brain myelination in development (Yakovlev and Lecours 1967; Kinney and others 1988), and showed that the later a white matter region completed myelination or the longer it took to myelinate, the greater was that region's volume increase over controls (Herbert and others 2004; Fig. 5). Greater volume changes in later-myelinating white matter suggest a relationship with postnatal brain volume enlargement discussed above.

A lack of volume increase or even a relative reduction in the midsagittal area of the corpus callosum has been a consistent finding in autism, although regional bias has varied regarding which part of this structure is most affected (Egaas and others 1995; Piven and others 1997; Manes and others 1999; Hardan and others 2000; Herbert and others 2004). This means that the corpus callosum is disproportionately smaller than would be predicted given volume increases in more peripheral white matter (Jancke and others 1997), which may contribute to a reduction in interhemispheric connectivity and thus an increased tendency to lateralize functions (Lewis and others 2004). Indeed, a widespread increase in cortical asymmetry, predominantly in a rightward direction, has been documented (Chiron and others 1995; Herbert and others 2005).

Neurobehavioral Correlates

Insofar as its clinical impact has been assessed in some studies, large brain size has not appeared to have clinical correlates (Lainhart and others 1997; Miles and others 2000), whereas in others, it has appeared to be more common in higher-functioning individuals (Gillberg and de Souza 2002; Dementieva and others 2005). Brain enlargement is not always considered in studies of brain-behavior relationships, although mentioned in introductions to articles, it is often left aside at the point of model-building or hypothesis design, not finding its way, for example, onto lists of potential brain correlates of behavioral endophenotypes (Dawson and others 2002). There have been two reports of a relationship of large-scale brain size measures to cognitive and diagnostic variables. Deutsch and Joseph (2003) found that head circumference was not associated with language or executive functioning and was also not related to either verbal or nonverbal IQ taken individually. However, it did correlate with a discrepancy between nonverbal and verbal IQ, where the nonverbal score was higher (Deutsch and Joseph 2003). Akshoomoff and others (2004) found that four volumetric variables (cerebellar white matter volume, area of anterior and of posterior cerebellar vermis, and cerebral white matter) contributed to two discriminant functions that separated high-functioning autism, low-functioning autism, and controls (with a mean age of 6 years) from each other.

Large brains, even if the volume increase has nonuniform features, represent a pervasive rather than regionally localized abnormality. As such, they invite association with more generalized processing abnormalities that have been modeled as underlying the observed and defining behaviors, such as weak central coherence (Shah and Frith 1993), the idea that autism is a disorder of late or complex information processing (Minshew and others 1997), underconnectivity (Just and others 2004), and the framing of autism as a neural information processing disorder (Happe and others 2001; Belmonte and others 2004). However, these constructs have not to date been evaluated directly in relation to large brain size or

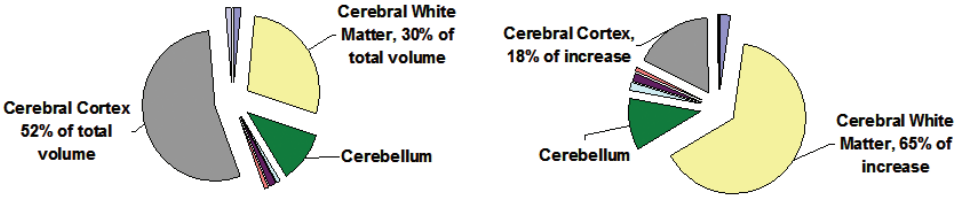

Fig. 2. In the pie chart on the left, total brain volume is divided by the percentage contribution of each major brain structure to the overall volume. In the pie chart on the right, the volume differences between autism and controls are broken out by contribution of each structure. Whereas cerebral cortex comprises 52% of total brain volume in autism, it contributes only 18% to the brain volume increase over controls. On the other hand, whereas cerebral white matter comprises 30% of total brain volume, it contributes 65% of the volume increase over controls. The scaling of brain volumes in autism is thus nonuniform in comparison with controls.

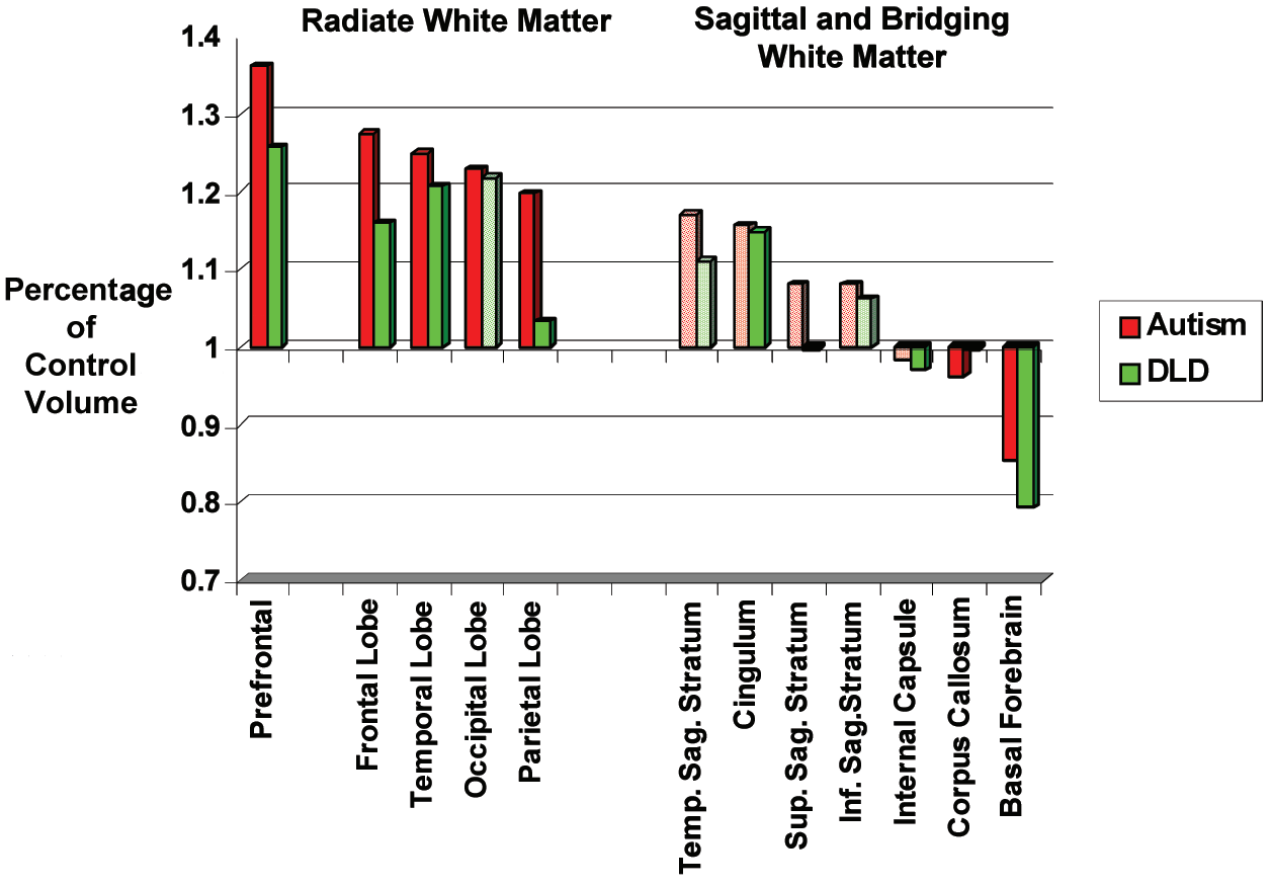

Fig. 3. Radiate but not deep (sagittal or bridging) white matter volume (see Fig. 4) is increased in a group of high-functioning autistic boys and of boys with developmental language disorder (DLD). Volumes are shown as a percentage of control volume. Solid bars are statistically significant; speckled bars are not statistically significant. Radiate white matter in all four lobes is significantly larger in autism than controls, whereas in DLD, three lobes (sparing parietal) are similarly affected. Prefrontal white matter has an even greater enlargement over controls than frontal lobe white matter in both groups. In the deeper sagittal and bridging, white matter volumes are with one exception not larger than controls, and basal forebrain is smaller for both groups (Herbert and others 2004).

to major components of this size increase such as white matter.

Genetics, Environment, and Large Brains

At the current time, we can only speculate about the role genes may play in autism macrocephaly, as no specific genetic mechanisms for autism have been identified at this time. There are a variety of genetic syndromes whose phenotype includes macrocephaly, but although it is conceivable that these syndromes may involve mechanisms related to those underlying autism, only a few (e.g., neurofibromatosis 1 and Sotos syndrome) have both macrocephaly and autism as part of their phenotypic profile, whereas for the most part, genetic syndromes that involve an increased incidence of autism are not known to feature macrocephaly (McCaffery and Deutsch, "Macrocephaly and the Control of Brain

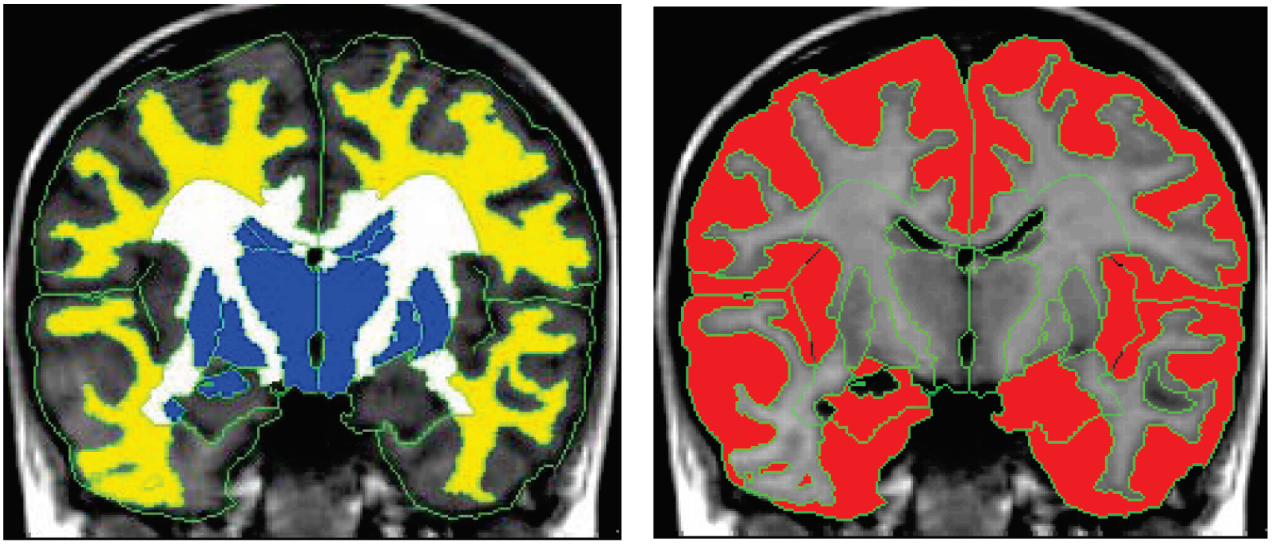

Fig. 4. In the figure on the right, radiate white matter, whose enlargement is graphed in Figure 3, is shaded yellow, while sagittal and bridging matter are shaded white. In addition, deep gray matter structures, shaded blue, are absolutely the same or slightly larger than but proportionately no different from controls (cerebellum and brain stem also fall into this category, but they are not visible on this slice). In the figure on the right, cerebral cortex and hippocampus-amygdala, which are shaded red, are absolutely no different from but relatively smaller than controls (Herbert and others 2003; Herbert and others 2004).

Growth in Autistic Disorders," unpublished manuscript). Nevertheless, it is worth exploring whether some of the more common autism-associated genetic syndromes could have hitherto unappreciated macrocephalic features or even comparable altered proportionality of brain tissue compartments; the neuroanatomy of many of these syndromes is not well characterized at the level of what we now know about autism. At the same time, given growing numbers of reports documenting increases in the numbers of autistic individuals, with no conclusive explanation for these increases (Fombonne 2003; Blaxill 2004; Newschaffer and others 2005; Palmer and others 2005), it is prudent to include environmental as well as genetic factors as potentially implicated in this endophenotype.

Underlying Tissue Changes

The finding of regional differentiation in white matter volumetrics has raised the question of what tissue changes might be driving this phenomenon. Some inferences can be made from volumes yielded by gray versus white matter tissue classifications. The dissociation of white matter from gray matter volumetric patterns (Herbert, Ziegler, Deutsch, and others 2003) and trajectories over time, with white matter enlargement being initially greater and persisting longer than cerebral or cerebellar cortical involvement, suggests that the white matter enlargement is less likely to be a function of an increase in neuronal number and more likely to be a consequence of changes intrinsic to white matter, such as increased myelination. Although this is only an inference, it is further supported by magnetic resonance spectroscopy data showing less rather than more n-acetylaspartate (NAA) in autistic brains (Friedman and others 2003); because NAA is associated with neurons, a reduction of this metabolite suggests less rather than more neurons and axons.

Although diffusion tensor data have the potential to shed some light on white matter in autism, at the current time, there are limited data in this modality. These studies measure fractional anisotropy (FA), which relates to the extent to which diffusion of water is directionally constrained. Although myelin can constrain water diffusion directionally, FA is not specific for myelin, and caution must be used in interpreting FA data. In 2- to 4-year-olds, Piven's group reported that fractional anisotropy appears to be similar to what is found in control subjects several years older (Cascio and others 2005), whereas in another study involving teenagers, multiple clusters were noted of reduced fractional anisotropy in white matter adjacent to ventromedial prefrontal cortices, in anterior cingulate, in temporoparietal junctions, near the amygdala, in occipitotemporal tracts, and in the corpus callosum (Barnea-Goraly and others 2004).

Although studies are currently underway, at the current time, there is no neuropathological documentation of the microscopic changes associated with white matter enlargement, so although we can make circumstantial inferences, we cannot yet confidently attribute it to increases in myelination, axonal density, increased vascularization, or any other particular change.

Minicolumns

Casanova and others (2002) have published several reports of increased numbers of minicolumns with greater cell dispersion in autism. These data were derived from an analysis of digitized images of lamina III in several Brodman areas. Minicolumns, defined as vertical clusters of large neurons delimited by cell-sparse areas on either side, were detected using a com-

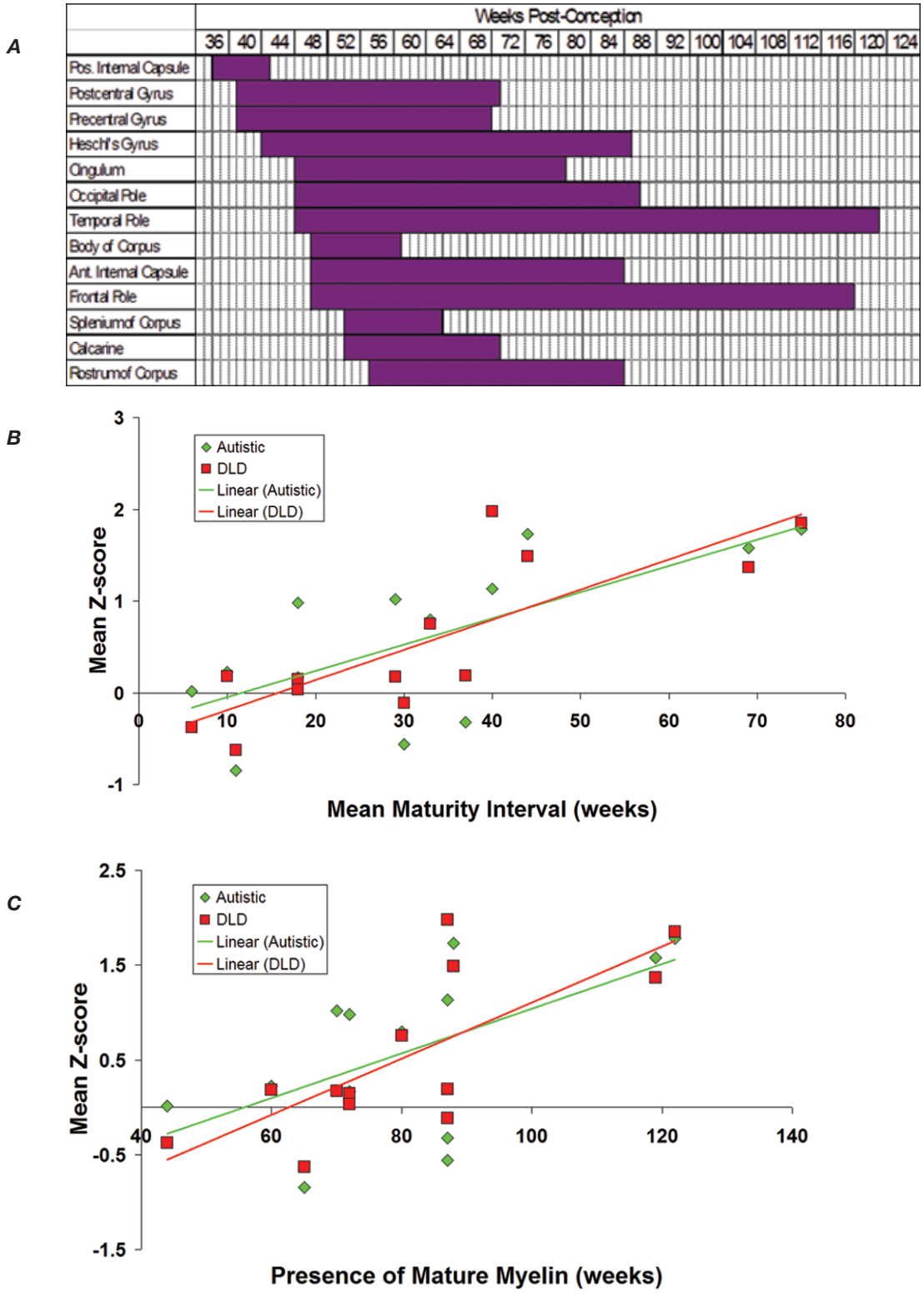

Fig. 5. *A*, Myelination has different times of onset duration and completion by brain region. This figure illustrates regions with neuropathological data regarding a myelination timetable whose structures could be discerned using white matter parcellation. Weeks are indicated postconceptionally. Figures 5*B* and *C* illustrate regression analysis to indicate the relationship of timing and duration of myelination with the extent of volume increase over controls. The longer myelination takes (Fig. 5*B*, "mean maturity interval") and the later the presence of mature myelin is noted (Fig. 5*C*, "presence of mature myelin"), the greater is the volume increase (shown as mean Z score) compared with controls. This relationship was found for both autism and developmental language disorder (DLD) subjects (Herbert and others 2004).

puterized column detection routine. Out of the nine autistic cases, four had brain weights greater than 2 standard deviations above the mean (though one of these had edema), but increased brain weight did not appear correlated to the width of minicolumns, although the analysis was limited as brain weights were available for only one control. However, implications of an increased number of narrower columns also exist for connectivity related both to interneurons as they are affected by columnar alterations (Casanova and others 2003) and to an altered number and proportion of short- and long-range connecting fibers in the brain (Casanova 2004). Although the number of minicolumns is determined early in gestation, there is considerable architectural resculpting in subsequent periods of development, and nitric oxide insufficiency has been proposed as one potential causal mechanism for autism that could cause narrow minicolumns postnatally (Gustafsson 2004).

Neuroinflammation

For years, it had been assumed that autism did not involve inflammatory processes, as there was no evidence of consistent inflammation or gliosis on neuropathological examination (Kemper and Bauman 1998) and MRI images were typically clinically (if not volumetrically) normal. Scattered neuropathological findings of inflammatory changes and gliosis (Guerin and others 1996; Bailey and others 1998) were not subject to detailed analysis to further characterize these changes. Recently, however, using immunocytochemistry, cytokine protein arrays, and enzyme-linked immunosorbent assays, neuroinflammation has been demonstrated in a series of autistic brains as well as in CSF from autistic individuals (Vargas and others 2005; Fig. 6). This inflammation was found in individuals ranging from 5 to 44 years of age. It appeared to reflect involvement of the CNS innate but not adaptive immune system, as it involved activation of microglia and astroglia but not lymphocytes; whereas cytokine profiling showed elevations in a number of cytokines, particularly macrophage chemoattractant protein–1 and tumor growth factor–β1. The measures by which this inflammation was established may be questioned due to conditions of death and to imperfect matching of subjects with controls. Nevertheless, the consistent trend across measures and the prior context of multiple studies detecting peripheral immune abnormalities in autism suggest that this is a phenomenon deserving of reflection and further examination. The neuroinflammation appears to be of a character quite similar to that found in Alzheimer disease. The failure to detect this abnormality on MRI in autism is thus paralleled by the insensitivity of MRI to the microscopic changes documented in Alzheimer disease at the other end of the life course.

It also appears that accompanying these neuroinflammatory findings are signs of oxidative damage (C. Pardo, personal communication, November 2004), signs of which are also being discerned in studies of autistic brain tissue by other investigators (Perry and others 2005), as well as in peripheral tissue samples (Chauhan and others 2004; James and others 2004). Taken together, these findings represent pathophysiology of a chronic and persistent type, a different class of abnormality than the type of fixed alteration in cellular organization in tissue that is immunologically quiescent that has hitherto been assumed.

With the neuropathological documentation of neuroinflammation in autistic brains and CSF, the field of interest has considerably widened regarding potential relevant alterations in tissue composition. This finding adds several further dimensions to the axes along which brain changes need to be mapped in autism. The issue is no longer simply a developmental alteration in proportions of gray and white matter tissue compartments in intrinsically healthy tissue, as has been an unstated but implicit assumption in the bulk of volumetric discourse. Now, additional consideration needs to be given to the possible roles played by metabolic alterations of inflammation and oxidative stress, the as yet unidentified drivers of these metabolic alterations, and the extent to which microglial and astroglial activation and inflammatory cytokines and chemokines might alter both brain structure and brain function.

At the current time, the study of brain inflammation in autism is just beginning, and its relationship to brain volume has not yet been investigated. Because documentation of neuroinflammation was accomplished in brain sections rather than whole brains and across a range of ages, even had brain weights been reported, the sample would have been insufficient to make a judgment about the correlation of inflammation and macrocephaly. And as noted, although we have established that white matter contributes disproportionately (though not exclusively) to brain enlargement, the underlying tissue changes contributing to this enlargement have not yet been specified microscopically. However, it is likely that macrocephaly and neuroinflammation co-occur, given that some degree of neuroinflammation was found in every autistic tissue specimen examined and given that macrocephaly, although not universal, is quite common. The question thus arises as to whether these are coincidental comorbidities or whether there is some intrinsic relationship between the two phenomena regarding underlying mechanisms.

In anticipation of studies to come, one might consider a variety of potential ways that neuroinflammation could contribute to overall and white matter volume increase. The simplest is directly by an increase in cell size or by swelling. If activated microglia and astroglia take up more space and there is a sufficient number of them, this could contribute to a subtle but measurable volume increase. Such a volume increase might be enhanced by associated increases in tissue water or other inflammation-associated tissue changes or by a compensatory increase in vascularization to overcome possible inflammation-related impairment of perfusion. All such changes would need to be fairly subtle and diffuse—

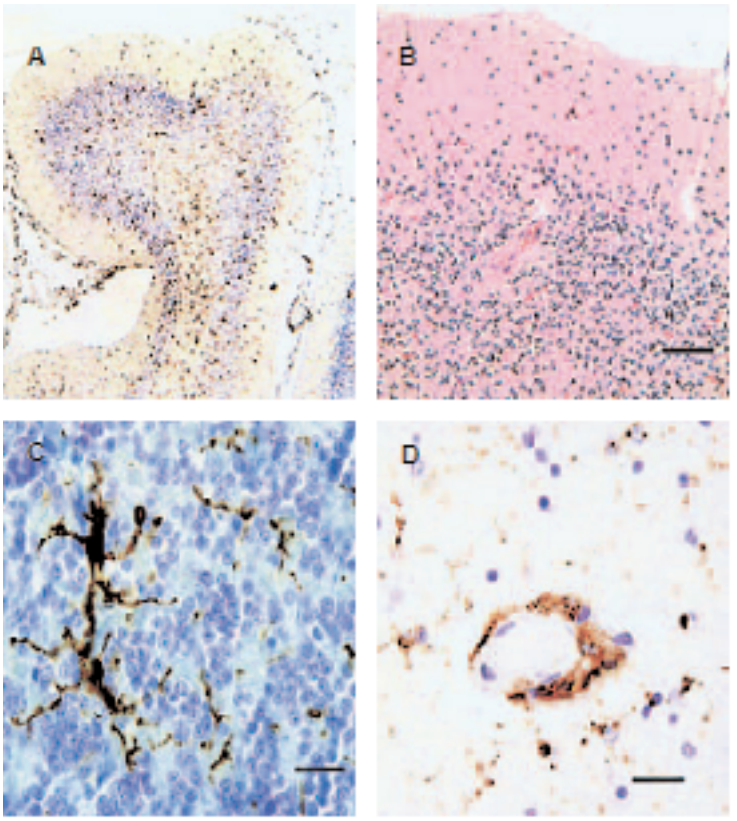

Fig. 6. Neuroinflammation in autism. *A*, Microglial activation in cerebellar folia. *B*, Marked Purkinje cell layer and granular cell layer neuronal loss. *C*, Activated microglia in the granular cell layer. *D*, Perivascular macrophages and microglia (Vargas and others 2005).

enough to be detected in neuropathological investigation but not pronounced enough to be detected by standard MRI neuroimaging protocols.

A second potential route of influence of neuroinflammation on brain volume is through cytokine or chemokine alterations in signaling pathways modulating development (Hamilton and Rome 1994; Ambrosini and Aloisi 2004; Cartier and others 2005). Other signaling pathways modulating development could conceivably also be altered by whatever underlying condition might be triggering the neuroinflammation, which is presumably itself a secondary rather than a primary process.

A further possibility is that neuroinflammation and associated increased oxidative stress could alter the chemical milieu of the brain, leading, for example, to increased excitotoxicity that in turn would increase cortical arousal. There are some suggestions in the literature that increased neuronal and axonal activity is associated with increased oligodendrocyte activity (Barres and Raff 1993). This cascade of effects could conceivably lead to an increase in myelination.

Could neuroinflammation be a type of pathophysiology that early in development might lead to brain enlargement but at a later developmental time might contribute to a slowing of brain growth? It could be that neuroinflammation leads to a set of tendencies in development that are countervailing in relation to each other. Although mechanisms such as those listed above could early on increase volume, persistent inflammation and oxidative stress could over time lead to impaired cell health or apoptosis. This may be an explanation for the observation of Bauman and Kemper that cytological findings differed by age, with younger subjects having larger cells whereas older subjects had smaller cells in portions of the inferior olive and cerebellar nuclei (Kemper and Bauman 1998). That these cell size changes between younger and older subjects were found only locally and not pervasively in these postmortem specimens suggests that they might not be implicated in global volumetric trends, but it could relate to regionally enhanced vulnerability to this class of pathophysiology (Boulanger and Shatz 2004).

Neuroinflammation and microgliosis are complex in both cause and function and have adaptive as well as maladaptive features (Wyss-Coray and Mucke 2002). In degenerative disorders, they can arise as a response to cellular debris related to progressive failure in a component of cell metabolism disrupted by the genetic error that underlies the disorder. But aside from distinct genetic variants such as Rett syndrome, we are not seeing compelling evidence of cumulative progress of an inborn genetically based metabolic error in autism. Although the decrease in relative volume and the decrease in cell size in certain regions with increasing age suggests a process that involves some losses in cell volume and/or number over time, these changes are mild compared with those in degenerative disorders, so that other mechanisms need to be considered. Various classes of environmental factors are candidate contributors to this picture. Oxidative stress, brain inflammation, and microgliosis have been much documented in association with toxic exposures including various heavy metals,

pesticides, and air pollution (Kim and others 2002; Zurich and others 2002; Campbell 2004; Ling and others 2004; Shanker and others 2004; Filipov and others 2005). The burgeoning research domain of low-dose persistent toxic exposures may well prove relevant here (Welshons and others 2003). A number of investigators are studying how autism and other developmental disorders could also be mediated by immune or infectious factors, either chronic subclinical infection or the sequelae of infection in the past (Hornig and Lipkin 2001; Patterson 2002; Dalton and others 2003; Shi and others 2003). For example, a mouse model of in utero influenza viral infection is associated with the postnatal development of macrocephaly, although the longer-term brain size trajectory is not documented in this study (Fatemi and others 2002). In these settings, genetics might play a role in modulating the threshold for vulnerability (Pletnikov and others 2002; Hornig and others 2004). Volumetric changes from such factors might involve a combination of local and scaling alterations (Herbert and Ziegler 2005). Further research is needed here.

Energy Metabolism and Perfusion Abnormalities in a New Light?

In the setting of this new class of tissue data in autism, it may be worth revisiting earlier findings regarding abnormal energy metabolism and perfusion in autism. The early 31P-MRI spectroscopy finding of Minshew and others (1993) showing evidence suggesting increased membrane degradation and decreased high-energy phosphate compounds in dorsolateral prefrontal cortex, as well as the increase in lactate found by Chugani and others (1999), may be related in some way to the pathophysiological abnormalities or underlying triggers also associated with neuroinflammation and oxidative stress, as may be the increased choline/creatine ratio found by Sokol and others (2002), which may be associated with membrane degeneration or increased cellular proliferation. The many reports of brain hypoperfusion, reviewed elsewhere but too numerous to enumerate here (Starkstein and others 2000), could conceivably also rest on an underlying inflammatory pathophysiology, such as the perivascular microgliosis documented by Vargas and others (2005) or conceivably by disturbed energy metabolism. Interestingly, although almost all studies reported hypoperfusion and none reported hyperperfusion, these articles focused only on correlating the localization of hypoperfusion with neuropsychological deficits but not on disease mechanisms; now, emerging questions bring to the fore the issue of underlying tissue pathophysiology.

Functional Effects: Reduced Brain Integration or Connectivity

One possible effect of brain enlargement might be a pervasive decrement in brain integration. The phenomenon of large brains had not yet been identified in autism when the pervasive finding of reduced covariance of brain regions with each other was reported; this was in fact one of the earliest neuroimaging findings in autism. An early positron emission tomographic study by Horwitz and others (1988) showed reduced correlations of resting cerebral metabolic rates among regions in autistic brains. Although only 4 of 31 regional cerebral metabolic rates for glucose differed between groups, 70% of the 861 possible correlations had lower values in the group with autism; moreover, there were significantly fewer robust correlations in the group with autism than in the control group (Horwitz and others 1988). Following Horwitz, Starkstein and others (2000), in a single-photon emission computed tomography study demonstrating low perfusion in mentally retarded autistic subjects, calculated a correlation matrix with 42 correlations and found that the control group had 26 of 42 correlations (62%) above this r value, as compared to only 8 of 42 correlations (19%) for the autistic group.

This approach has recently been expanded from resting brain activity to studies of functional brain activation. Two recent functional MRI studies, one of sentence comprehension (Just and others 2004) and one of working memory (Koshino and others 2005), showed a reduced degree of synchronization of the time series of functional activation between the various participating cortical areas. In the first of these articles, Just and others (2004) reported consistently lower functional connectivity in autism as compared with controls, with this measure tracking parallel in autism to controls but at a lower level (Fig. 7). Just and others placed this phenomenon in the framework of "underconnectivity theory," which is a formulation of processing abnormalities in autism, such as earlier "weak central coherence" or "impaired complex processing" models, but one whose formulation more clearly links brain function with behavioral function. This linkage strongly suggests a connection to underlying pervasive brain structural, perfusion, or chemical alterations, which calls for further exploration.

Although Just and others' (2004) experimental design and formulation were novel, when one reads between the lines of many functional neuroimaging studies in autism, one sees that although the attempt to illuminate the specificity of neural systems' impairment underlying the features of autism has yielded equivocal results (e.g., inconsistent results regarding ventral temporal activation in relation to face processing, e.g., Schultz and others 2000; Pierce and others 2001; Hadjikhani and others 2004; Dalton and others 2005), the data themselves suggest atypically distributed activations and reduced covariation or abnormal interregional coordination (Belmonte and Yurgelun-Todd 2003; Herbert 2004). Perfusion altered consistently in the direction of reduction could be a tissue-level facet of the same overall phenomenon. The frameshift of seeing coordination properties as figure rather than background to specific neural systems functioning makes it possible to bring these commonalities to light.

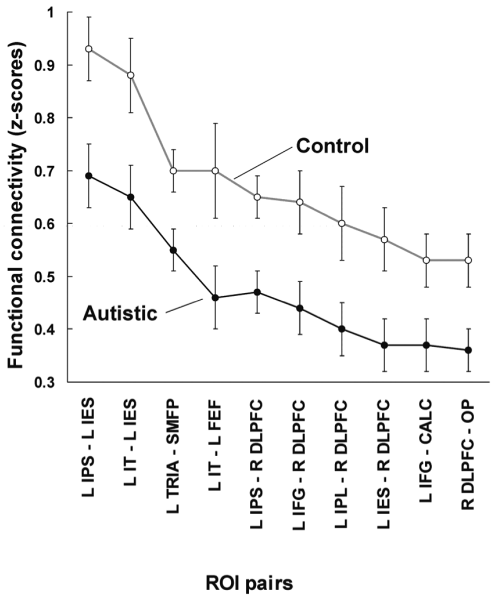

Fig. 7. "Underconnectivity" in autism. Functional connectivity between 10 region-of-interest pairs is consistently lower in autism than in controls but shows the same rank order (Just and others 2004).

Connectivity and Systems Vulnerability

At this early stage in the development of the research pursuit of pervasive abnormalities in autism, it becomes helpful to turn to modeling for guidance in hypothesis formation. A common thread among the pervasive deficit-oriented models already cited (e.g., weak central coherence [Shah and Frith 1993], impaired complex processing [Minshew and others 1997], underconnectivity [Just and others 2004], disordered neural information processing [Belmonte and others 2004], and neural network abnormalities [McClelland 2000; Cohen in press]) is a systems approach to the analysis of brain functioning. The idea that a pervasive impairment in connectivity or brain integration could underlie the autism behavioral phenotype is based on the idea that altered systems properties can produce specific and not just pervasive changes in features. In this model, the behaviors that define the autism phenotype are not independently aggregated components but rather interrelated features of altered systems output that emerge as a consequence of these processing and connectivity problems. From this point of view, the domains of functioning most dramatically affected will be those that are most dependent on highly coordinated associational processing (Fig. 8). Nuanced and pragmatically subtle language and social interaction, as well as the capacity for behavioral flexibility, which are the domains hit hardest in autism and whose impairment has constituted the definition of the disorder, will certainly suffer more strikingly. This impairment of integration has been formulated or modeled as a systems issue by a number of investigators. Cohen (in press) has proposed a neural network model in which either too many or too few neuronal connections, as documented in the neuropathological literature, would lead to overemphasis on specific details but an inferior capacity for generalization. Brock and others (2002) proposed that a reduction in the integration of specialized local neural networks in the brain caused by a deficit in temporal binding would lead to abnormal processing consistent with "weak central coherence." McClelland (2000) has proposed that hyperspecificity in autism derives from abnormalities in neural nets. These formulations bear substantial resemblance to lines of thought emerging in other disorders such as schizophrenia and Alzheimer disease and in cognitive neuroscience more generally, in which the notion is being explored that the manifestations of neurobehavioral disorders may derive from impaired cortical coordination dynamics (Bressler and Kelso 2001).

Implications of a Systems Formulation

This systems formulation of the cognitive neuroscience of autism has a number of implications. First, in addition to functions most highly vulnerable to reduced brain integration, many other functions will also suffer decrements, if in more subtle ways. The research program of Minshew, Just, and colleagues, pursuing this perspective, includes investigation of multiple domains to evaluate the evidence for impairments in complex processing, and they have interpreted impairments in working memory, abstract reasoning, postural control, and other complex functions in this manner (Minshew and others 2002; Minshew and others 2004; Koshino and others 2005).

Second, although traits may be specifically characterized, they may not be independently determined. From this perspective, the core impairment is regarded not as at the level of a set of independent traits with independent brain loci, biologies, and genes (Silverman and others 2002) but rather as at the level of an underlying processing or computational abnormality that has multiple functional consequences. The argument can be made that this is a more parsimonious approach to cognitive neuroscience and potentially also to the genes and environmental factors implicated in underlying etiology of the disorder.

Third, the processing impairment is based on underlying tissue abnormalities whose pathophysiology underlies underconnectivity. Here it is important to comment that pervasive tissue and processing changes can easily coexist with localized abnormalities, for instance, if a relevant receptor is more highly expressed in certain regions, as is the MHCI receptor in limbic system and cerebellum (Boulanger and Shatz 2004). Moreover, as the heterogeneity of such tissue and related metabolic pathophysiology is better characterized, it may prove more useful than behaviors in identifying autism clinical and genetic subgroups.

Fourth, once the physicality of the underlying tissue abnormalities is considered, there is no reason to presume that the pathophysiology is confined to the brain. Although there is a great deal of heterogeneity to the

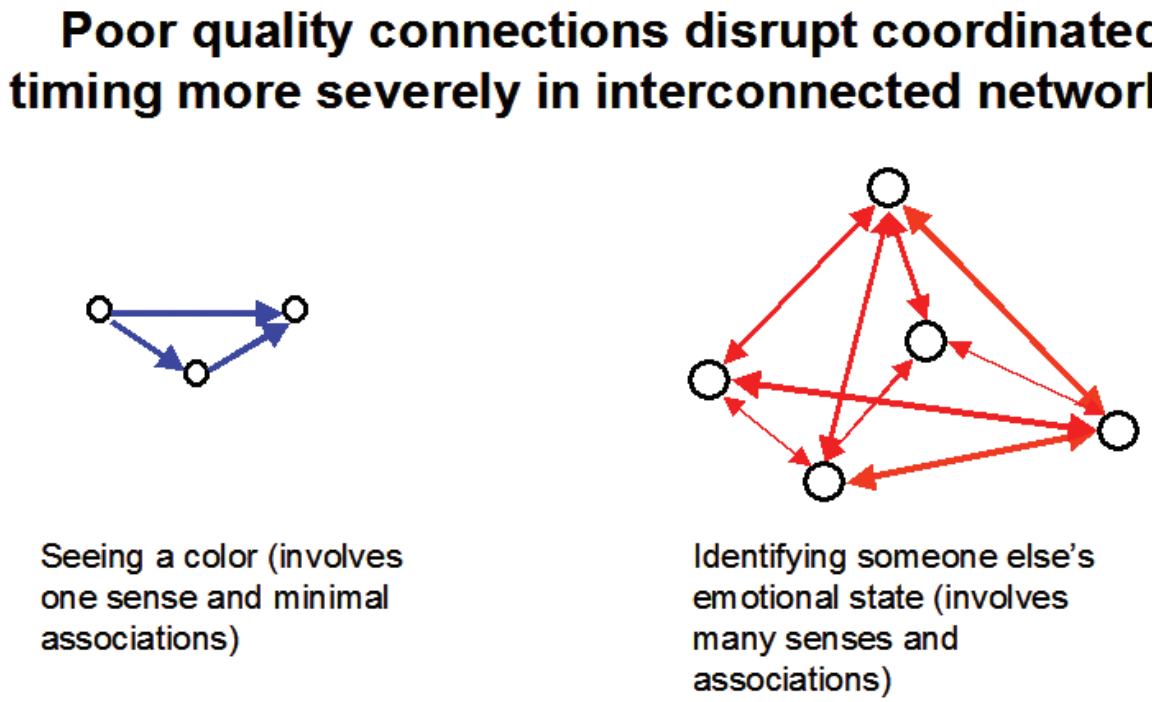

Fig. 8. Poor-quality connections disrupt coordinated timing more severely in interconnected networks. Functions involving connections among a small number of nearby areas are less vulnerable to impaired connectivity than are functions that integrate information across many areas that are widely distributed throughout the brain.

medical complaints that frequently accompany autism, there are common threads that may indicate common or related molecular and cellular mechanisms between body and brain. For instance, the pathophysiologies of inflammation, oxidative stress, and excitotoxicity are greatly linked, and it appears these types of mechanisms are implicated in the brain as well as in some of the sensory and sleep regulation, epilepsy, immune, and gastrointestinal complaints commonly seen in autism.

Fifth, some of the tissue pathophysiology and consequent processing abnormalities now being identified in autism are final common pathways that may eventuate from a broad range of genetic, metabolic, toxicological, immune, infectious, and even stress-related triggers. The systems-perturbation-derived specificity of autistic behaviors can thus plausibly rest on a great heterogeneity of origins. It is thus no wonder that it has been so difficult to find either genetic or metabolic biomarkers for autism.

Sixth, the dynamics described above are not likely to be confined to the syndrome of behaviors we now call autism. Hebert and others have documented brain size (Herbert, Ziegler, Makris, and others 2003), overall and radiate white matter enlargement (Herbert and others 2004; Figs. 2, 3, 4, and 9), and widespread asymmetry shifts (Herbert and others 2005) that are highly similar in high-functioning autism and developmental language disorder (DLD) or specific language impairment (SLI; Fig. 8). Neither total brain volume nor anatomical abnormalities had been addressed in DLD/SLI in earlier studies due to an a priori assumption that relevant abnormalities in a language disorder would be confined to language-associated areas of the brain. But theories of pervasively slow processing have emerged in DLD/SLI that bear a suggestive similarity to underconnectivity theories in autism, and both theories imply an anatomical association with more widespread brain abnormalities. Moreover, a growing body of literature has documented that DLD/SLI is in fact not specific but involves more subtle impairments across the board (Hill 2001; Webster and Shevell 2004). In addition, a connection to immune system abnormalities has been a persistent subtheme in childhood language disorder research (Behan and Geschwind 1985; Benasich 2002; Dalton and others 2003). Finally, there appears to be both functional and genetic overlap between these two groups (Kjelgaard and Tager-Flusberg 2001). Intriguingly, similar lines of thought about overlap are also emerging in relation to other disorders such as Tourette syndrome (Becker and others 2003; Plessen and others 2004).

Seventh, both the newly appreciated chronicity of some of the underlying pathophysiology and the pervasiveness of the connectivity abnormalities open new horizons for seeking potential treatment targets. Inflammation, oxidative stress, excitotoxicity, and other neurochemical changes and their triggers open a range of possibilities for research into potential treatment targets. Characterizing the connectivity abnormalities underlying behavioral manifestations may allow a sharpening of behavioral therapies. More fundamentally, the awareness that the brain as well as medical conditions of children with autism may be conditioned by chronic bio-

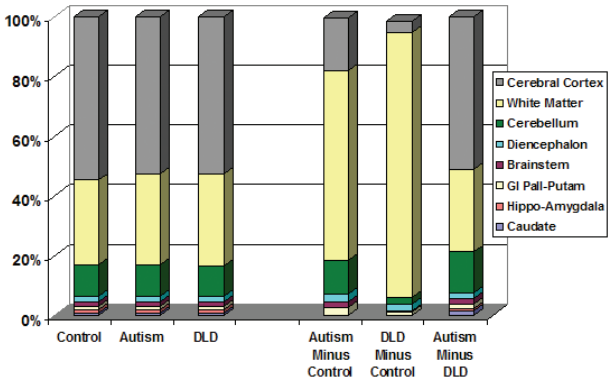

Fig. 9. Autism and developmental language disorder (DLD) brains are similar to each other but different from controls. In the three bars on the left, the proportions of cerebral cortex, white matter, cerebellum, and other smaller brain structures are illustrated for the whole brain, similar to the pie chart for autism in Figure 2. In the three bars on the right, the contribution of each brain structure to the volume increase of autism over controls (left bar of this group) and DLD over controls (middle bar of this group) are shown to be nonuniform with respect to controls: white matter disproportionately accounts for bigger brains in autism (65%) and even more so in DLD (88%), where the overall volume increase is less. In the rightmost bar, which analyzes the contribution of each structure to autism's size increase over DLD, the volume increase in autism is uniform with respect to DLD; that is, all parts of the autistic brain are (on average) larger than in the DLD brain proportionately (i.e., to the same degree) in both groups (Herbert and Ziegler 2005).

medical abnormalities such as inflammation opens the possibility that meaningful biomedical interventions may be possible well past the window of maximal neuroplasticity in early childhood because the basis for assuming that all deficits can be attributed to fixed early developmental alterations in neural architecture has now been undermined.

Conclusion

The conundrum of large brains in autism thus appears to be giving up its mystery and instead is leading us toward convergence upon a fruitful reformulation of both pathophysiology and function in autism. This reformulation points toward more coordinated interdisciplinary research agendas and raises hopes of more integrated understanding. It also opens prospects of prevention and particularly of ameliorative intervention. Thus, understanding may reasonably soon be translated into impact, which is the ultimate goal of the biomedical enterprise.

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