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Brain overgrowth in autism during a critical time in development: implications for frontal pyramidal neuron and interneuron development and connectivity

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Abstract

While abnormalities in head circumference in autism have been observed for decades, it is only recently that scientists have begun to focus in on the developmental origins of such a phenomenon. In this article we review past and present literature on abnormalities in head circumference, as well as recent developmental MRI studies of brain growth in this disorder. We hypothesize that brain growth abnormalities are greatest in frontal lobes, particularly affecting large neurons such as pyramidal cells, and speculate how this abnormality might affect neurofunctional circuitry in autism. The relationship to clinical characteristics and other disorders of macrencephaly are discussed.

Keywords: Autism; Brain development; Frontal cortex; Pyramidal neurons; Head circumference

1. Introduction

The normal baby is born with limited processing and behavioral capacity because neural circuitry is still sparse in many brain regions, most especially those that are responsible for higher-order cognitive, speech, language, social, emotional, and self-awareness functions (Huttenlocher, 2002). During the first years of life, the emergence of functional capacity depends heavily on the creation and refinement of circuitry generated by an unparalleled burst of synaptogenesis, neuronal growth and differentiation, and myelination coupled with learning and experience-based processes that select and stabilize adaptive connections. These essential growth and selection processes follow regionally ordered and precisely timed sequences, and as a result neurobehavioral functions emerge and become refined in an orderly hierarchical fashion during the first postnatal years (Herschkowitz, 2000; Huttenlocher, 2002; Quartz and Sejnowski, 1998).

It is during these first years of life that behavioral symptoms of autism first appear. Single case reports, retrospective studies and parental comments suggest that subtle motor, sensory, attention and social behavioral abnormalities may be present (but clinically undetected) as early as the first or second year of life (Adrien et al., 1992; Osterling and Dawson, 1994; Dawson et al., 2000; Maestro et al., 2002). By 2–3 years of age, failures to achieve normal language and social developmental milestones commonly become substantial enough to alert parents and physicians that a child might have autism.

Brain maldevelopment must precede, underlie and trigger these first, early behavioral abnormalities. Due to the relatively late age of diagnosis, however, research directed at the first years of life has been sparse. Instead most past brain research has focused on the older child and adult with autism.

However, as reviewed below, new MRI studies of toddlers and studies that utilize head circumference as an index of brain size during the first years of life have collectively identified a striking phenomenon in autism. Namely, infants and toddlers with this disorder may suffer from a delimited period of excessive brain growth that occurs during the first

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years of life, a period of time that coincides with the onset of autism symptoms. Further, this period of overgrowth is followed by an abnormally reduced rate of brain growth. The evidence reviewed in this paper also indicates that abnormal overgrowth may be more pronounced in frontal lobes, which undergo growth and selection processes later and longer than other areas of the brain. As presented below, we hypothesize that cortical systems (e.g., frontal cortex) with a more protracted developmental timetable for synaptogenesis, dendritic growth, circuit formation and myelination may be more adversely impacted by the growth dysregulation than those that mature rapidly and early (e.g., primary visual cortex). Thus, growth dysregulation will most strongly affect regions mediating higher-order social communication, emotional processing, language and cognition, while regions mediating more low-level functions would be relatively spared. Large integrative and projecting pyramidal neurons that normally require many years of slow growth, such as those in frontal cortex, would be maldeveloped which may result in a reduction in long-distance connectivity and top-down control signaling, while abnormal increases may occur in local and short-distance connectivity and processing. Maldevelopment of large frontal interneurons, such as chandelier cells, could undermine the development of selective inhibitory control.

Although the cellular bases of the early growth pathology in autism are unclear, it has previously been hypothesized the early brain volume increases might be due to excessive numbers of cerebral cortical neurons and/or glial cells (Courchesne et al., 2001) and to excessive number of minicolumns (Casanova et al., 2002). New studies, mentioned very briefly below, appear to add support to these hypotheses.

In this paper we first briefly review earlier seminal studies regarding brain size in autism, and then present recent evidence that points to a process of early brain overgrowth that precedes the clinical onset of autism and coincides with the first subtle signs of autistic behavior. We then argue that newly described brain growth dysregulation occurs during a critical time in the formation of high-order cortical circuitry, and that the underlying mechanisms for it disrupt the development of frontal pyramidal neurons, interneurons and circuitry. This, in turn, causes the dysfunction in social and emotional communication, language, attention and cognition. Lastly, we discuss the clinical implications of the recently described early brain growth abnormality in autism.

2. Research has provided evidence that a subset of older children and adults with autism have abnormal brain size

Over the decades, tools used to investigate brain size in autism have included CT and MRI based brain volume measurement, postmortem brain weight and head circumference. Strong interest in the possibility that brain size abnormalities can occur in individuals with autism was sparked by early postmortem (Bailey et al., 1993) and MRI studies (Piven et al., 1995). Since then, many studies have shed light on the phenomenon.

2.1. MRI and autopsy studies: overall whole brain enlargement occurs in some adolescents and adults with autism

There are now a number of reports of brain volume in adults and adolescents with autism using neuroimaging techniques, predominantly MRI. One study reported that brain volumes were 6% greater than normal in autistic adolescents and adults (Piven et al., 1995). However, some other studies reported no difference in overall brain size between normal subjects and autistic adolescents or adults (Aylward et al., 1999; Creasey et al., 1986; Haznedar et al., 2000; Howard, 2000; Jacobson et al., 1988; Hardan et al., 2003).

Using postmortem techniques, one study of four autistic brains reported abnormally heavy weight (1820 g) for one of the cases (Bailey et al., 1993). A recent postmortem study included those four plus 17 other cases in the literature, and found megalencephalic weights in 14% of cases and normencephalic weights in 86% (Courchesne et al., 1999). Of these 21 total cases, almost all were adolescents or adults. In reviewing the literature on autism brain weights, Courchesne et al. (1999) pointed out that confusion about whether autism weights are or are not heavier than normal is due primarily to the common reliance on normative data from Dekaban and Sadowsky (1978). While the mean weights reported in the Dekaban and Sadowsky (1978) study are consistent with many other normative brain weight studies, the error term is not, being about one twelfth (about 10 g) that of all other normative studies (about 120 g). It appears that the error term reported in Dekaban and Sadowsky (1978) study was the error of the mean and not the standard deviation. Thus, past autism studies that used the standard error term from Dekaban and Sadowsky (1978) may have unwittingly over-reported the number of megalencephalic cases among adolescent and adult postmortem cases.

In sum, past MRI and postmortem research has revealed striking megalencephaly in a small but important percentage of older autistic patients. That research, however, also demonstrated that brain enlargement in autistic adolescents and adults is not a common feature.

2.2. Head circumference studies and the relationship to overall brain size

Studies of head circumference (HC) in autism also raised the question of whether some subset of patients have an abnormal brain size. Those studies consistently reported 10–30% of older autistic children and adults as having macrencephaly (Davidovitch et al., 1996; Deutsch and Joseph, 2003; Fidler et al., 2000; Fombonne et al., 1999;

Ghaziuddin et al., 1999; Lainhart et al., 1997; Miles et al., 2000; Stevenson et al., 1997; Gillberg and de Souza, 2002; Woodhouse et al., 1996). Even studies published almost 30 years ago hinted at the phenomenon of abnormal HC in autism (Steg and Rapoport, 1975; Walker, 1977), although at that time diagnostic standards and normative comparison values were different than they are today.

Another fundamental question raised by these HC studies of autism was whether HC was a useful indicator of the size of the brain within the head. Recent MRI studies have directly addressed that question. One study measured both HC and brain volume in children and adults with autism; in autistic children both HC and brain volume are both greater than normal, but in autistic adolescents and adults only HC was larger than normal, brain volume was not (Aylward et al., 2002). Another study has directly tested the correlation between HC and MRI-derived brain volume at different ages. It reported that in both autistic and normal subjects, HC was an accurate index of brain volume in young children, but a poor index at progressively older ages (Bartholomeusz et al., 2002). Thus, at older ages, HC may be an interesting but rather imperfect reflection of an earlier developmental growth deviance.

Overall, then, review of past MRI, postmortem and HC studies of autism, it can be concluded that among older children, adolescents and adults with autism a small percentage do have abnormally enlarged brain size and HC, but the great majority do not have substantially enlarged brain size. Until recently, however, evidence regarding early brain growth in autism has been missing. Also missing has been evidence of age-related changes from early ages to adulthood. New studies have begun to fill these gaps in developmental information on autism.

3. New MRI and HC studies show early brain overgrowth then premature cessation of growth in autism

New MRI and HC studies have addressed these questions about early brain development in autism for the first time and discovered a process of early brain overgrowth in the majority of autistic children that is soon followed by abnormally slow growth in brain regions that mediate higher-order neurobehavioral functions.

3.1. The first years of life in autism: early brain overgrowth

3.1.1. MRI studies

In the first MRI study of brain size in autistic toddlers, brain volume was 10% greater than normal, with 90% of the autistic toddlers having volumes exceeding normal average (Courchesne et al., 2001) (Fig. 1). Another recent study also found brain volumes at about10% greater than normal in autistic children aged 3–4 years (Sparks et al., 2002). A new MRI study separately analyzed the neuroanatomy of 2–5-year-old girls and boys with autism, and found that, like the boys, girls with autism had significantly abnormally enlarged whole brain volume (Bloss and Courchesne, submitted for publication). These studies raised the question of when brain enlargement begins in autism. This has been addressed by retrospective studies of head circumference during the first years of life.

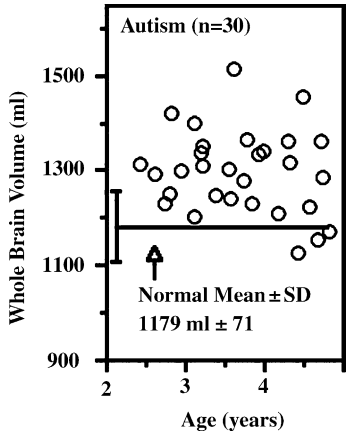

Fig. 1. Plot of individual whole brain volumes (volumes in cm^3) of 30 2–4-year-old autistic boys. Shows that 90% of the autistic boys had brain volumes larger than normal average (shown as solid horizontal line with normal mean for that age range being 1179 ± 71 cm^3). From Courchesne et al. (2001).

3.1.2. Birth head circumference in autism

Prospective studies of the developing brain in infants with autism have yet to be done. Most retrospective studies of autism, however, have found that, the mean HC in autism is similar to or slightly smaller than normal average at birth (Hultman et al., 2002; Courchesne et al., 2001, 2003; Lainhart et al., 1997; Stevenson et al., 1997), but one study reported it to be somewhat larger (Gillberg and de Souza, 2002). Average HC at birth in autism was 34.7 cm in Gillberg and de Souza (2002), 34.41 cm in Lainhart et al. (1997), and 34.65 cm in Courchesne et al. (2003); the HC data in Hultman et al. (2002) indicates the average for their sample would also be in this same range. Thus, it appears that different research groups have found similar average newborn HC size in autism. Despite extraordinarily similar values from different studies of HC in autistic male infants, researchers have concluded that newborn autism HC is larger than normal (Gillberg and de Souza, 2002), not different from normal (Lainhart et al., 1997) and smaller than normal (Courchesne et al., 2003). Differences in conclusions between studies appears to be due to differences in choice of clinical HC norms (Swedish norms, Roche norms and CDC norms), not in the actual size of the head and therefore the size of the brain at birth in autism. Since HC is a good indicator of brain size at young ages, we conclude that at birth the autistic brain is definitely *not* substantially larger than normal in most of the individuals with this disorder.

On the other hand, it seems to also be true that a very small percentage of autistic newborns have an extremely large HC. For example, excessive HC at birth in autism was reported for 4 of 42 (Gillberg and de Souza, 2002), 5 of 206 (Mason-Brothers et al., 1990), 3 of 51 (Lainhart et al., 1997), and 1 of 15 (Courchesne et al., 2001) cases. Particularly telling is that among a sample of autistic children who were pre-selected on the basis of having clinical macrencephaly, only 1 of the 18 had macrencephaly at birth; 1 of the 18 had microcephaly at birth and the remaining 16 were normencephalic (Stevenson et al., 1997). Thus, normencephaly at birth is the most common finding among autistic patients, even those who as children have extremely large, macrencephalic head size.

In sum, it appears that at birth in autism HC is within normal range or is slightly smaller than normal for the majority of autism cases. Macrencephalic HC at birth in autism uncommon, occurring in perhaps 6% of all autism cases. Perhaps this very small subgroup with macrencephaly at birth represents a distinctly different etiology from the majority of autism individuals, or perhaps they represent individuals in whom the developmental timing of the overgrowth pathology, but not the underlying neurobiology, differs from the majority of autism individuals.

3.1.3. Study of early growth in head circumference in autism

To examine brain growth before the age of clinical diagnosis in autism, Courchesne et al. (2003) analyzed longitudinal changes in HC from birth to 2 years of age in a small sample of autistic infants. In comparison to CDC norms, HC at birth in the autism group was at the 25th percentile. After several months, head size increased rapidly, reaching the 84th percentile by 6–14 months of age (Fig. 2) (Courchesne et al., 2003). In this study, it was also reported that 59% of the infants diagnosed with Autistic Disorder showed a HC increase of 2 S.D. or more across the first year of life as compared to 6% of normal infants from the well-known Fels Longitudinal Study.

This early and brief period of abnormally accelerated HC increase in these autistic infants was largely concluded by about 2 years of age because HC at 15–28 months was only 2 percentile points higher than at 6–14 months (Fig. 2). These HC findings imply that by 2 years of age, brain volume in autism is significantly greater than normal average. This HC conclusion is compatible with the recent MRI studies mentioned above that reported brain volumes are 10–12% greater than normal in 2–4-year-old autistic children.

Among the autism spectrum disorder (ASD) infants in the Courchesne et al. (2003) study, those with a diagnosis of autism had a substantially greater rate and amount of HC increase than those with a diagnosis of pervasive developmental disorder not otherwise specified (PDD-NOS). This result was consistent with a previous prediction (Courchesne et al., 2001) that brain overgrowth may be earlier, more rapid and more substantial in more severely affected autistic children. The 2003 study also tested for correlations between HC in the first year of life and later neuroanatomical outcome. It found that in the autistic infants HC size at birth and HC overgrowth by the end of the first year of life were strongly correlated with abnormal cerebellar and cerebral volumes, respectively, at 2–5 years of age.

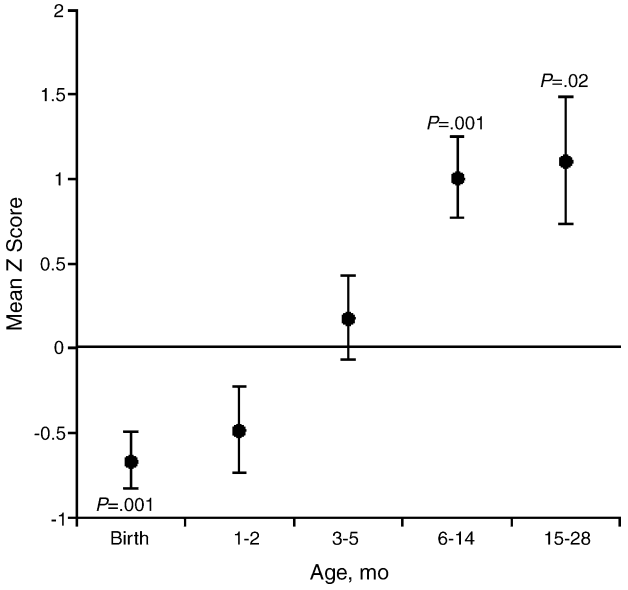

Fig. 2. Age-related changes in head circumference during infancy in autism spectrum disorder shown. At birth and at 1–2 months of age, head circumference in a longitudinal autism spectrum disorder group was statistically significantly below the Centers for Disease Control and Prevention (CDC) mean for healthy infants, but by 6–14 months of age, it was more than 1.0 S.D. (84th percentile) above the mean for healthy infants. The CDC mean of healthy infants at each age is 0. Error bars are SEM. Reproduced with permission from Courchesne et al. (2003).

In sum, the evidence from recent HC and MRI studies indicates an early, relatively brief and age-limited process of *abnormally accelerated brain growth* during the first years of life. To our knowledge, this is the first evidence of brain maldevelopment *in process* before the behavioral manifestation of the disorder. Further studies are needed to more precisely delineate the ages of onset, peak, and cessation of this process.

3.2. Premature cessation of further brain growth: MRI evidence

Cross-sectional and meta-analysis studies show that following the developmentally early, yet brief period of brain overgrowth, the rate of growth slows or ceases, and so the autistic brain by adolescence and adulthood is not larger than normal average.

First, using a cross-sectional design, Aylward et al. (2002) reported brain volume in autism to be larger than normal in 8–12-year-olds, but not in adolescents and adults. Also using a cross-sectional design, we found abnormally enlarged brain volume in 2–4 but not 5–16-year-old autistic

children (Courchesne et al., 2001) and not in adult autistic patients (Carper and Courchesne, submitted for publication). Also, seven recent MRI studies reporting results of single age ranges have also reported statistically non-significant differences from normal in autistic brain volume at ages 4–11 years (Carper et al., 2002), 5–13 years (Kates et al., 2004), 7–11 years (Herbert et al., 2002, 2003, 2004), 12–18 years (Aylward et al., 2002), 8–45 years (Hardan et al., 2003), 17–47 years (Rojas et al., 2002) and 18–43 years (Carper and Courchesne, submitted for publication). An eighth study (Tsatsanis et al., 2003) did not statistically test for brain volume differences but did report autistic and normal brain volumes for the age range of 18–40 years; autistic brain volumes differed from normal by less than 1%.

Second, in a meta-analysis study, Redcay and Courchesne (submitted) examined brain size through the lifespan from birth to old age in autism. MRI brain volume, postmortem brain weight and HC data from more than twenty autism publications were analyzed. Results showed that in autism, maximum brain size difference from normal average rapidly grows within the first 2 years of life, peaks by 2–4 years (reaching roughly 10% in volume and 15% in weight), and then declines across childhood; by adolescence and adulthood the difference from normal size is about 1% (Redcay and Courchesne, submitted).

4. A combination of abnormal excess and reduction at the microstructural level

When considering the effects of growth aberration on microstructural development in autism, then, early overgrowth is but one factor to consider. Others are premature arrest of growth and the consequent distortion of spatiotemporal sequences and interactions among different cortices. Thus, a mix of effects may well be observed at the neuronal level in autism, with some findings reflecting processes and consequences of accelerated and excessive growth, and others reflecting arrested, truncated or absent differentiation and growth.

New postmortem studies support this hypothesis. In lectures at a recent conference on stereological studies of the same set of autistic and control brains, in the autistic cases there was an increase in cerebral cortical neuron numbers (Schmitz, personal communication, November 13, 2004) but a decrease in cerebellar Purkinje neuron numbers and a reduction in volume of the cerebellum (Wegiel, personal communication, November 13, 2004). Previous studies by Kemper and Bauman (1998) have observed increased neuron density and decreased cell size in the anterior cingulate cortex of 8 of 9 in autistic patients. Taken together, then, it appears that autism may involve too many cells that are too small in cerebral cortex. An excess of neurons means and excess of axons, which could help explain the overgrowth of cerebral gray and white matter volumes during early development in autism.

We recently reported in a pilot study evidence of abnormally narrow minicolumns with small cell size in dorsal, mesial and orbital frontal cortices but not in primary visual cortex in autism (Buxhoeveden et al., 2004). This is the first study to examine frontal regional differences in minicolumn size in autism and to compare minicolumn size between autism at the youngest age (3 years) and at adulthood; about 1500–2000 minicolumns were measured per autism case. Our finding of reduction in minicolumn size throughout frontal cortical regions extends the initial report by Casanova et al. (2002) who also found abnormally narrow minicolumns in the one frontal area they examined, area 9. Interestingly, Casanova et al. (2002) also reported narrow minicolumns in autism in temporal areas 21 and 22, and MRI studies show that, like frontal cortex, temporal cortex is enlarged at 2–4 years of age in autism, but fails to grow thereafter (0% change from 2–4 years to 6–8 years in autism versus 17% in normals) (Carper et al., 2002).

The presence of smaller than normal minicolumns in a larger than normal sized brain has lead to the speculation that there could be an excess of minicolumns in autism (Casanova et al., 2002), which would implicate mechanisms regulating symmetrical cell division during the second trimester. Alternatively, perhaps cerebral cortex is too thick and so, minicolumns taller, but not more numerous, than normal. Excess neurons per minicolumn could result in abnormally thick cortex, and of course, it could be that there is an excess of both numbers of minicolumns and neurons per minicolumn. These and other possibilities remain to be quantitatively tested.

Nonetheless, the essential point is that minicolumns including their surrounding neuropil space are underdeveloped in widespread regions of frontal cortex in autism (Buxhoeveden et al., 2004). The minicolumn, which has a vertical organization, is a fundamental unit of information processing in cortex providing fine-tuning within cortical columns. Minicolumns are adapted to meet diverse information processing needs, and this functional differentiation occurs during the course of development. Thus, in autism, the underdevelopment of minicolumns in frontal cortex likely signals the failure of the normal emergence of a diversity of highly specialized functional units that are necessary for the refined processing of and learning about information critical to higher-order functions.

Conversely, the presence of *normal* minicolumns in primary sensory cortex may signal that the autistic brain retains the capacity for detailed and refined processing of lower-level visual information. Thus, we find that cortical areas of impaired and spared minicolumns parallels behavioral areas of impaired and spared function in autism, and coincide with those areas with late and protracted versus early and rapid neuronal and minicolumn development. To our knowledge this is the first evidence of such regionally specific parallels between cortical cytoarchitecture, function, and developmental timetables in autism.

5. Early brain growth abnormalities are deleterious because they occur during a critical time in human development

Overgrowth and arrest of growth in autism occur during a critical time in human brain development. These early years of life are characterized by exuberant generation of neural circuitry, and are also a time during which the baby's brain first interacts with and learns from its world. Normal growth and experience cause a transformation from sparse and nascent to dense and powerful neural circuitry during these first years of life, and recognition of this phenomenon has lead to the view that it is a time of exceptional vulnerability (Dobbing, 1981; Kinney et al., 1988) as well as opportunity (Bateson, 1979) for neurofunctional organization.

At the beginning of this period, the normal newborn has sparse neural circuitry and limited processing and behavioral capacity (Quartz and Sejnowski, 1998; Herschkowitz, 2000; Huttenlocher, 2002). This neuronal developmental condition is particularly pronounced in cortices that will ultimately mediate the most complex cognitive and social functions of any life form on earth, regions of frontal and temporal cortex. For example, in the newborn baby dendritic arbors for layer three pyramidal neurons in frontal cortex are a mere 3% of mature size. From birth through the next few years of life, brain volume quadruples (Blinkov and Glezer, 1968; Courchesne et al., 2000), cortical synapse counts increase dramatically (e.g., by a factor of 10 in area 17 from birth to 6 months) (Huttenlocher, 2002), dendritic arbors of pyramidal neurons grow tremendously in extent (e.g., by 3–16 times from birth to 24 months depending on layer and region) (Huttenlocher, 2002), volume of cortical pyramidal cells may double or quadruple depending on region and layer (Blinkov and Glezer, 1968), the corpus callosum nearly triples in size and cerebral axonal myelination increases rapidly (Kinney et al., 1988; Huttenlocher, 2002). The rate of change during these early years can be dramatic; in visual cortex synapses are generated at the rate of 100,000 per second during the first months of life (Huttenlocher, 2002). Change can also be especially protracted; in frontal cortex, the dendritic arbors for layer three pyramidal neurons, which are only 3% of mature size in the newborn, are still only 50% by 2 years of age, and do not reach 100% until the end of childhood. Thus, from the first year and for several years thereafter, processes of neuronal differentiation, dendritic and axonal growth, myelination and synapse formation create complex and extensive cerebral circuitry from which higher-order mental and behavioral capacities emerge.

It is a doubly special period in development because for the first time in a baby's life there is a rich interaction between intrinsic mechanisms that regulate growth, neural selection, neuronal differentiation, synapse formation, and connectivity on the one hand and the human and non-human environment on the other (Quartz and Sejnowski, 1998). These two fundamental processes of exuberant growth and brain-environment interaction play out in a dynamic milieu capable of making widely different selections and eliminations of neuronal design. As a result of these generative and selective processes, neurobehavioral functions ranging from movement to self-awareness emerge and become refined in an orderly hierarchical fashion across years.

These processes obey strict regionally and functionally specific timetables (Huttenlocher, 2002; Herschkowitz, 2000). Posterior cerebral cortical systems (e.g., visual cortex) develop earlier than frontal systems, and cerebral systems mediating more basic-level functions (e.g., audition) develop earlier than those mediating higher-order functions (e.g., speech, language comprehension, social communication, and self-awareness) (Fig. 3) (Huttenlocher, 2002). At birth, the length of pyramidal cell dendritic arbors in layer 5 is 33% of full maturity in visual cortex but only 11% in frontal cortex, and by 2 years of age they are 93% of mature size in visual cortex but only 62% in frontal (see Table 1.3 in Huttenlocher, 2002). Still more years must pass before pyramidal dendritic arbors reach full size in frontal cortex (Fig. 4). Myelination follows the same functional hierarchical pattern with basic-level systems developing earlier than higher-order association systems (Kinney et al., 1988) (Fig. 5). As compared to posterior regions, frontal cortex undergoes synapse formation later and for a longer period of time. As compared to visual cortex, frontal cortex also develops far larger pyramidal neurons with far more synapses (about 100,000 versus about 20,000) and far greater size of dendritic (e.g., 7558 versus 3000 μm in layer 5) and axonal arbors and axonal projections (Huttenlocher, 2002).

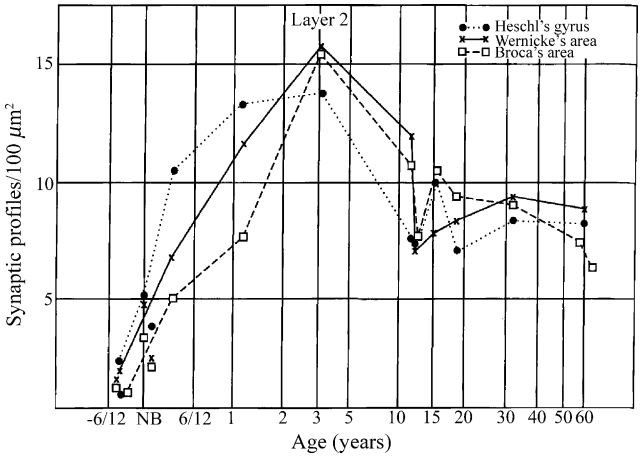

Fig. 3. Synapse density as a function of age in three cerebral cortical regions important for language processing. Shows a functional hierachical developmental sequence with synaptogenesis in primary auditory cortex preceding that in Wernicke's area which mediates language comprehension, which in turn precedes synaptogenesis in Broca's area, a frontal region mediating speech production. Shows that neurodevelopmental timetables may sometimes reflect functional hierarchical sequences and that frontal cortical areas may develop later than some posterior regions. Dotted line = Heschel's gyrus (auditory cortex) in temporal lobe; solid line = - Wernicke's area in left temporal lobe; dashed line = Broca's speech area in the left frontal lobe. From Fig. 2.7 in Huttenlocher (2002).

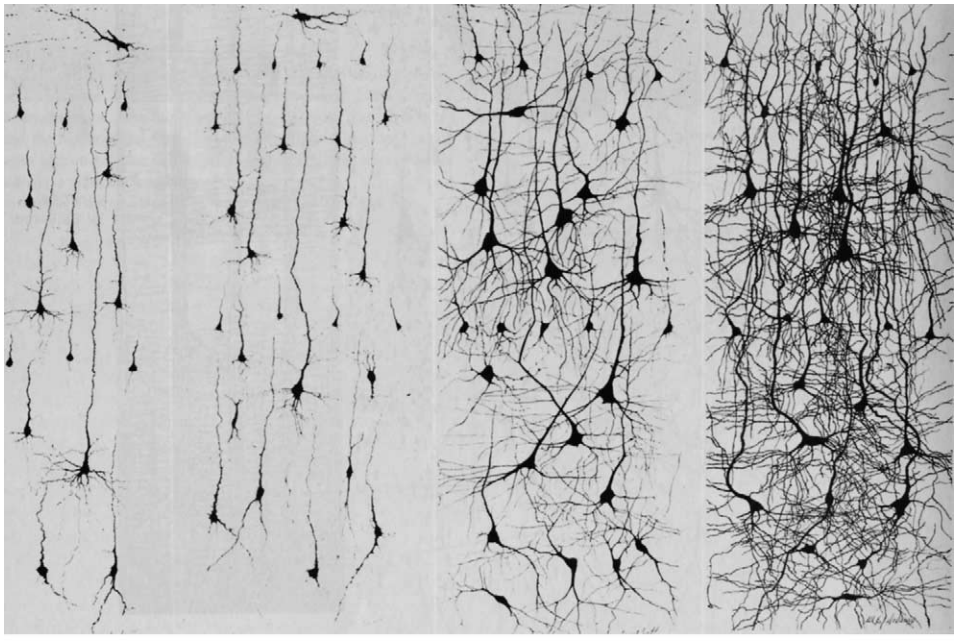

Fig. 4. Golgi-stained sections showing growth of pyramidal neuron soma and dendrites in middle frontal gyrus. The normal newborn has sparse neural circuitry, and then with increasing age, there is a tremendous increase in the complexity of dendritic arborizations. In this frontal cortical area, the dendrite arbors for layer three pyramidal neurons, which are only 3% of mature size in the newborn, are still only 50% by 2 years of age, and do not reach 100% until the end of childhood (see text). From Nolte (Nolte, 1993) whose figure combined panels from Conel, JL: The postnatal development of the human cerebral cortex. Cambridge, Mass., Harvard University Press.

We theorize that autistic behavior emerges as a result of brain growth dysregulation that disrupts and distorts the precise spatiotemporal orchestration of intrinsic and experience-based processes of neural development and circuit formation. As a result of the temporally brief and delimited period of overgrowth followed by premature arrest of growth, the brains of infants with autism compress into a brief time what ordinarily takes many years to complete. In contrast, the developing human brain is designed to benefit from an extended period of synaptogenesis, myelination, dendritic and axonal growth, and circuit formation that is carefully guided and shaped by experience (Quartz and Sejnowski, 1998). Indeed, in the normal case it is across infancy and childhood that sensations, emotions, thoughts and actions shape the formation of neuronal structure from synapses to systems. A multitude of experiences, including hundreds or even thousands of repetitions of some forms of experience such as speech and language, leads to the creation of new synapses, reinforcement of others and elimination of still others, slowly but inevitably leading to more refined and adaptive neural organization.

We suggest, therefore, that the overly brief period of excessive growth of the infant autistic brain disallows this signature attribute of the normally developing human brain.

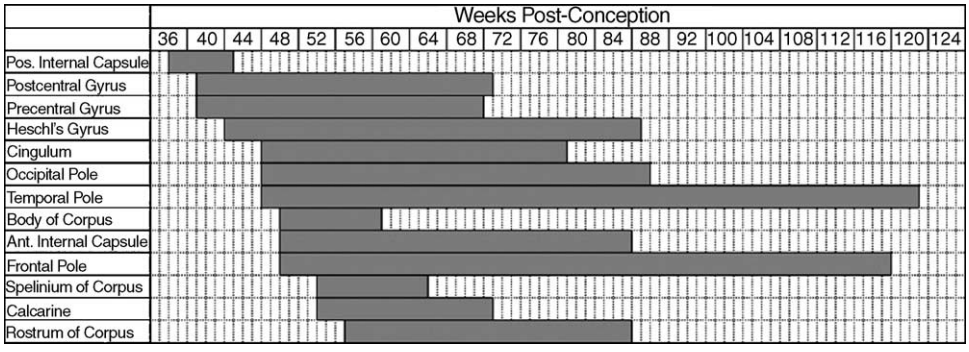

Fig. 5. Myelination timetable for selected regions. Shows that myelination follows a functional hierarchical pattern with basic-level systems developing earlier than higher-order association systems. Gray bars start with myelination onset and end with myelination maturity, as defined in Kinney et al. (1988) as the week when 50% of subjects meet maturity criteria. The length of the bar represents the myelination interval. From Kinney et al. (1988).

6. Regional differences in growth abnormality

Investigations have revealed that the abnormal brain overgrowth in autism in the first years of life is due to enlargement of cerebral, cerebellar and limbic structures (Carper and Courchesne, 2000; Carper et al., 2002; Courchesne et al., 2001; Sparks et al., 2002). Increases in both gray and white matter volume have been reported, with especially pronounced increases in cerebral (by 18%) and cerebellar (by 39%) white matter (Courchesne et al., 2001). The amygdala has also been reported to be enlarged in autistic children ages 3–4 years (Sparks et al., 2002) and 7–12 years (Schumann et al., 2004), but not in adolescents or adults with autism (Aylward et al., 1999; Pierce et al., 2001; Schumann et al., 2004).

Within the cerebrum, frontal and temporal lobes were reported to have the greatest growth deviation (Carper et al., 2002) (Fig. 6). Within the frontal lobes, especially deviant were dorsolateral and medial frontal cortex (Carper and Courchesne, 2005) (Fig. 7), both regions being well-known for their role in higher-order cognitive, language, speech and social functions. In contrast, occipital lobes were not significantly different from normal average (Carper et al., 2002) (Fig. 6). Interestingly, Bloss and Courchesne (submitted for publication) found that for several structures including whole brain, frontal cortex and temporal cortex, abnormal enlargement was greater in girls than boys with autism.

Consistent with this evidence of marked developmental abnormality of dorsolateral frontal, medial frontal and temporal regions, Levitt et al. (2003) found in autistic 11-year-olds anterior and posterior shifting of several frontal and temporal sulci, with the greatest deviation from normal being superior frontal, inferior frontal and superior temporal sulci and the Sylvian fissure. Herbert et al. (2002, 2004) found that autistic 7–11-year-olds had abnormal anatomic asymmetry in language-important inferior dorsolateral frontal cortex (Herbert et al., 2002), and that within cerebral white matter, the subregion with the greatest deviation from normal was radiate white matter underlying prefrontal cortex and the least was that in occipital lobes (Herbert et al., 2004). The first DTI study of autistic children reported abnormalities in white matter diffusion patterns in medial and dorsolateral frontal regions, temporal lobes, temporoparietal junction and anterior regions of the corpus callosum, but abnormality was not detected in occipital regions (Barnea-Goraly et al., 2004). New microstructural (Buxhoeveden et al., 2004) and neuroimaging studies (Buxhoeveden et al., 2004) also find no evidence of abnormality in occipital cortex.

In the first MRI studies of age-related changes in the autistic brain during early childhood and adolescence, we found that cerebral and cerebellar white matter volumes increased 59% and 50%, respectively, in normals, but only 11% and 7%, respectively, in autism (Courchesne et al., 2001). Maximum brain size was reached in autism by about 3–5 years of age, about six to ten years earlier than normal. Maximum cerebral gray matter volume was reached in autism by 2–4 years of age, about 4–6 years earlier than normal. Carper et al. (2002) also found that frontal and temporal cortical gray matter increased by 20% and 17% in normal children between 2–4 years and 6–8 years of age, but changed by only 1% and −1%, respectively, in autism during this same critical developmental period. The dorsolateral subregion of frontal cortex increased by 27% from 2–5 years to 5–9 years of age in normals, but by only 7% in autistic patients (Carper and Courchesne, 2005). Thus,

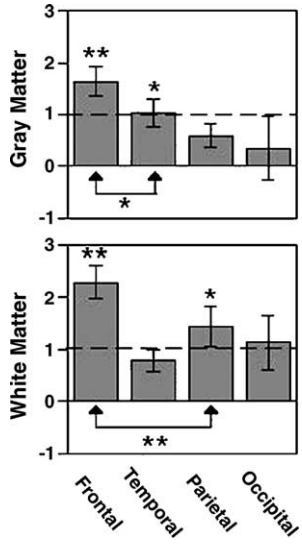

Fig. 6. In autistic 2–4-year-old children frontal lobes have the most abnormal enlargement of white and gray matter volumes. For each white and gray matter region, volumes were converted to z-scores for each 2–4-year-old autistic child based on the means and standard deviations of normal children of the same age. "0" on the y-axis indicates the normal mean and y-axis values indicate z-scores above this normal mean. Among autistic 2–4-year-old children, frontal and parietal white matter volumes and frontal and temporal gray matter volumes were each significantly larger (asterisks) than normal. Error bars are standard error of the mean for autistic children. Reproduced with permission from Carper et al. (2002).

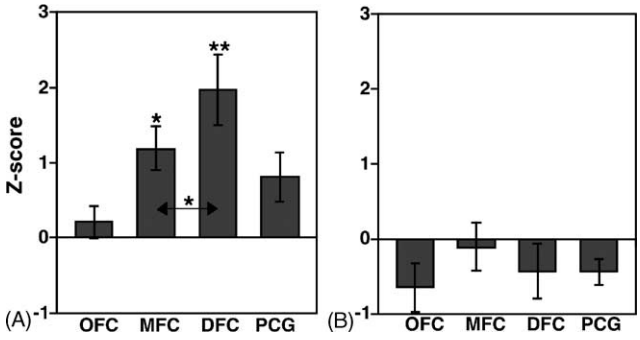

Fig. 7. Shows abnormal enlargement of frontal dorsolateral and medial cortex in 2–4-year-old autistic children (Panel A) but not in 5–9-year-old autistic children (Panel B). For the autistic children, volumes of each frontal region were converted to z-scores based on the means and standard deviations of normal children in the same age range. z-scores therefore represent relative degree of deviation from normal. The normal mean is defined as 0 with a standard deviation of 1. $^{*}p \leq 0.05$; $^{**}p \leq 0.005$. From Carper and Courchesne (2005).

regions that show the greatest early overgrowth in autism also show sharply reduced or arrested growth thereafter.

7. Frontal cortex is especially affected in autism

Frontal cortex development plays a particularly important and leading role in the emergence of higher-order functions, and, in autism, it is frontal cortex (especially medial and dorsolateral regions) and white matter that shows the greatest early overgrowth followed by arrest of growth (Carper et al., 2002) and the greatest deviation in radiate white matter (Herbert et al., 2004).

Evolutionarily, new frontal cortical neurons and circuitry (including fronto-neocerebellar circuitry) may be critical to the emergence of human-specific social and emotional functions, the very functions so profoundly disturbed in autism. We theorize that these very same leaps in neuronal-social evolution may simultaneously have created serious vulnerabilities to adverse perturbations, which can give rise to human-specific disorders such as autism. We argue, therefore, that the pivotal pathology in autism includes, but is not limited to, such evolutionarily novel neuronal structures and neurofunctional circuitry.

An illustrative example is anterior cingulate cortex (ACC), a brain region structurally and functionally abnormal in autism. Evolutionarily unique to humans and great apes are spindle neurons in ACC (Allman et al., 2002; Nimchinsky et al., 1999). Present in layer 5b, they are projection neurons four times bigger than pyramidal cells; their size correlates with encephalization, being smallest in gorillas and greatest in humans, and they receive from and project to a wide range of cortical and subcortical areas. Functional imaging studies show that the ACC is associated with integrating information with emotional overtones, anticipating and monitoring complex and potentially conflicting information, viewing personally important faces, and experiencing a feeling of social exclusion (Bush et al., 2000). In primates, socially meaningful vocalizations are elicited by electrical stimulation of this cortical area, and in humans ACC lesions lead to mutism, decreased motivation, decreased interest in novel information, and a reported reduced "will to act" (Allman et al., 2002). It has been theorized that this area played an important role in the evolution of social communication in primates (Nimchinsky et al., 1999; Allman et al., 2002). Although consensus on a single overarching theory of the functional role of the ACC remains is lacking, it does appear that the ACC is involved in continuously monitoring, integrating and interpreting the implications of complex higher-order cognitive, social and emotional information (Bush et al., 2000; Allman et al., 2002).

MRI, postmortem, diffusion tensor imaging, PET, fMRI and MR spectroscopy studies of autism consistently report abnormality in the ACC. For example, reported abnormalities have included reduced MRI volume in adult autistic patients (Haznedar et al., 1997); glial activation and molecular signs of neuroinflammatory reaction in child and adult autism postmortem cases (Vargas et al., 2005); abnormal white matter diffusion patterns in young autistic individuals (Barnea-Goraly et al., 2004); reduced functional activation in adolescent and adult autistic patients (Haznedar et al., 1997; Castelli et al., 2002; Hazlett et al., 2004); and reduced NAA (Friedman et al., 2003) and choline (Levitt et al., 2003) in young autistic individuals. Recently, Pierce et al. (2004) used fMRI to examine in autistic and normal groups the brain regions that are functionally responsive during the presentation of socially familiar and significant faces, such as mother, father, or sibling. In the autistic group, many posterior cortical areas, as well as the amygdala, activated normally. However, these same autistic patients showed an absence of medial frontal lobe activity extending from ACC into frontopolar area 10 (Fig. 8). In postmortem

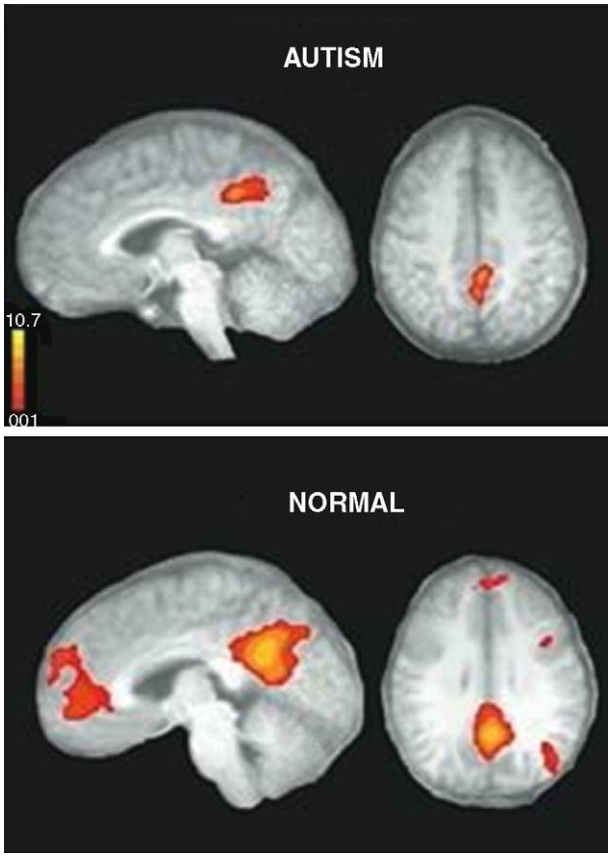

Fig. 8. FMRI activation to personally familiar faces (e.g., mother's face or sibling's face) vs. stranger faces in autism and normal groups; midsagittal and axial views shown for each group. Shows that, in response to socially significant faces (e.g., mother, sibling), normal subjects have strong functional activation in mesial frontal cortex extending from anterior cingulate cortex to frontopolar cortical area 10. This mesial frontal area was not significantly active in autistic patients despite the observation that, just like normal subjects, they did have significant fMRI activation in the posterior cortical and subcortical areas including posterior cingulate cortex, precuneus region, the fusiform face perception area (not shown), and the amygdala (not shown) just as did the normal group. The colors used in the functional maps represent p values associated with a t-statistic. Adapted from Pierce et al. (2004).

studies of autism, small neuron size and increased neuron packing density have been reported in the ACC, with the abnormalities being interpreted as evidence of arrest in development (Bauman and Kemper, 1994; Kemper and Bauman, 1998). Underdeveloped minicolumns have also recently been reported for mesial frontal cortex, which includes ACC (Buxhoeveden et al., 2004). In vivo MRI studies of medial frontal cortex, including the ACC, report abnormal enlargement by age 2–4 years (Carper et al., 2002). Not surprisingly, therefore, many have hypothesized that medial frontal cortex abnormality may play an important role in the social, emotional and cognitive deficits seen in autism (Damasio and Maurer, 1978; Frith and Frith, 1999; Haznedar et al., 1997; Mundy, 2003; Courchesne et al., 2004).

According to Allman et al. (2002), identifiable spindle neurons are few in number at birth (with as few as a tenth the adult number in infants) and increase dramatically in number across the first years of postnatal life in humans. Therefore, we raise the specific hypothesis that processes underlying the abnormal overgrowth in early life in autism disturb the development of spindle neurons by disrupting migration, survival after arriving in cortex, or molecular and microstructural differentiation and specialization.

8. Frontal pyramidal neuronal development and circuitry may be most affected

Although the cellular basis for the burst of overly rapid brain growth is unknown, the large integrative and projecting pyramidal neurons in frontal cortex would be especially vulnerable to early growth dysregulation because normally differentiation, expansion, and structural and molecular elaboration require years to reach completion in the human (Fig. 4) (review: Huttenlocher, 2002). As described above, pyramidal neuron dendritic arbors in frontal cortex double in size between the toddler years and about 8 years of age; deep layer pyramidal neurons in frontal cortex area 10 double in volume during that same period and full size is not achieved until adolescence. From birth through the toddler years, synapse numbers increase in frontal cortex, but the process of synapse selection and elimination takes another 6–10 years. This protracted time frame of cortical development leads to long-distance fronto-posterior and fronto-cerebellar connectivity and cortical coupling that is faster, more extensive and refined. Simultaneously, local processing becomes focal, efficient, and short-duration as maturation of higher-order cortex provides better top-down modulation and guidance. Eventually, reciprocal long-distance cortico-cortical interactions between frontal cortex and other more low-level and basic processing systems, become faster, synchronized, and more dynamic.

In autism, the rapid change in brain size followed by abnormally reduced growth bodes ill for all neuronal growth processes requiring extended periods of time. Large integrative and projecting neurons in frontal cortex as well as large inhibitory neurons such as chandelier cells would be especially vulnerable; not only is their normal developmental time-table more protracted than more posterior cortical regions as described above, but it is frontal cortex that suffers most extremely from excessive overgrowth in the first years of life in autism.

Our working hypothesis is that autism is a disorder of large neurons (cerebellar as well as cerebral) whose role is to integrate information from multiple, diverse and distant modalities (sensory, emotional, memorial, autonomic, motor, etc.) and to direct changes in attention and action that are most adaptive. Disruption of maturation of these neurons will cause aberrant local and long-distance neural connectivity. Dendritic arbors inadequately integrate the enormous variety of spatiotemporal signals sent from lower level systems, and axonal projections fail to communicate results back to the many systems that await further directions. Reduction in minicolumn size throughout frontal cortex that has been recently reported (Buxhoeveden et al., 2004) most likely reflects underdevelopment of pyramidal cells, their dendrite arbors, inhibitory interneurons such as chandelier cells and the intrinsic and extrinsic axonal connections that compose a minicolumn assembly.

With the maldevelopment of large integrative and projecting neurons, maturation of dynamic long-distance cortico-cortical and cortico-cerebellar signaling and top-down-control is significantly impaired. We predict that this abnormality will be most evident in frontal cortex, and so, higher cortical functions such as social and emotion processing and attention switching that demand concerted neural activity in multiple regions will be most impaired.

In contrast, short distance and local connectivity in frontal cortex will be abnormally increased. However, with abnormally increased local interconnectivity, reduced lateral inhibition as suggested by Casanova et al. (2002) and reduced top-down control, local neuronal activity would be expected to increase, spread across cortical patches faster and farther than normal, and last longer than normal. Our notion further suggests that the cortex in autism would have an impaired capacity to shut off such activity, thus reducing the ability to respond rapidly to new stimuli and processing demands. Deficient inhibitory regulation quite likely is due to dysfunction, underdevelopment or reduced numbers of inhibitory chandelier and basket cells. While some events might receive extensive and sustained processing and registration, awareness of ongoing context would be diminished and the ability to rapidly alter processing to respond to new and unexpected demands would be impaired as well.

In sum, we hypothesize that the maturation of large neurons, particularly those in frontal cortex, is seriously affected in autism, resulting in reduced or impaired long-distance cortico-cortical and cortico-cerebellar reciprocal connectivity. Fronto-posterior cortex and fronto-cerebellar

coupling and would be most affected. In contrast, we hypothesize enhanced ''local'' connectivity, which provides detailed information processing, but, with reduced long-distance connectivity, such detailed information fails to be adequately integrated into higher-order meaningful contexts. The most complex contexts of all to construct – social and emotional – would be most impaired because they (a) require the most diverse information modalities (sensory, emotional, memorial, autonomic, motor, etc.), (b) are information and action demanding, and (c) are the most variable and unpredictable from moment to moment. Because frontal and cerebellar cortices are most severely affected, the brain is left without key command systems that sort through low-level detail from multiple sources, extract the most important information about what is going ''right'' and ''wrong'', and select the next strategic attention and action steps in order to maintain or correct matters.

9. Temporal relationship between early brain overgrowth and emerging autistic behavior

Since evidence of massive brain overgrowth is present within the first year of life in autism, behavioral abnormalities should also be observable within this time period, or shortly thereafter. In fact, several studies have shown subtle and important behavioral abnormalities beginning within the first year. In a detailed single case report of an infant at risk for autism (later confirmed to meet the diagnosis of autism), motor, sensory and attention abnormalities were seen within the first few months of life (Dawson et al., 2000). In contrast, during this same time period, the infant was also described as cooing, cuddly and socially smiling. Thus, in this infant, there appeared to be a dissociation between attention, motor and sensory development on the one hand, and social development on the other, with social development appearing surprisingly normal during the early months. However, by the end of the first year, normal social expressiveness and responsiveness had disappeared, and autistic social abnormalities were in evidence. The precise time period that marks the decline of social responsiveness in autism is unclear. Retrospective analyses of home videos taken during the first year of life suggest that by 6 months of age autistic infants view and respond to non-social objects to the same extent as normal babies, but spend significantly less time viewing and responding to people (Maestro et al., 2002). In other studies, 1-year-old autistic infants showed less pointing, less responding to their name and less social orienting than normal control infants (Adrien et al., 1992; Baranek, 1999; Osterling and Dawson, 1994). By 18–30 months, abnormal behavior usually becomes clinically noticeable, with the most commonly reported concerns including absence or loss of speech, deviant or absent social responsiveness, and aberrant responsiveness to and interest in the infant's environment (Lord et al., 2000).

9.1. The onset of abnormal brain overgrowth may trigger dysfunction in the "social brain"

A temporal relationship between the onset of rapid brain growth and the derailment of social development in autism may exist. In the autistic infant described by Dawson et al. (2000), developmentally emergent social behaviors were present and not noticeably abnormal during the first few months of life. For example, at 2.5 months the infant ''was socially responsive, smiled responsively, and made vocalizations'', and at 4 months he ''made a lot of vocalizations during play and responded to social interactions from adults by smiling and cooing'' (Dawson et al., 2000, pp. 301). These early months of seemingly normal social behavior in the infant precede the peak period of accelerated brain overgrowth we observed (Courchesne et al., 2003). By or before 1 year of age, normal social behavior in this infant was entirely gone. Our research has shown that by this time, the pathological growth process has largely concluded. Thus, we hypothesize that autistic social behavior deficits are due to either neural abnormalities involved directly in the brain overgrowth or to those that precede and trigger it. To understand the brain bases of autistic social behavior deficits, therefore, it will be necessary to identify the neural events preceding and/or underlying early brain overgrowth in autism.

10. Clinical relevance of early brain overgrowth in autism: early identification of autism

Detecting autism at the earliest possible age is of the utmost importance. Based on what is known about mechanisms of brain plasticity and learning there is virtually unanimous agreement that early treatment can have a significant impact on the capabilities of children with autism. Indeed, several clinical studies of early intervention for young children with autism illustrate this point (Green et al., 2002; Rogers, 1996). As promising as early intervention treatments are, they typically do not begin until a child with autism is well into the toddler years. Developmental neurobiology has shown that plasticity is more evident and extensive in the younger brain in contrast to the older. Therefore, a realistic inference is that treatments for children with autism would be even more effective if they were initiated within the first year of life. However, the strategies for detecting autism within the first year of life remain elusive. As described above, using retrospective data, scientists have succeeded in finding differences between normal infants and infants later diagnosed as autistic in attention, social, and motor behaviors. However, for the average parent or practitioner, these abnormalities are usually not glaring enough to be detected until after the child's first birthday, and often not until much later. Furthermore, many infants, who will not develop autism, may show minor deviations in social, attention and motor

development during the first few months of life. Therefore, it does not seem that diagnosis within the first year of life, based on behavior alone will reach mainstream clinical practice anytime soon.

Fortunately, for the first time, practitioners may be able to utilize evidence of early and extreme brain overgrowth as a red flag for identifying children who may need further careful behavioral attention and possibly formal evaluation. While identifying children with autism based solely on this single attribute is not possible, the presence of a sudden and extreme jump in head size during the first year of life may eventually prove to be clinical useful when carefully combined with sensitive tests of behavioral symptoms consistent with autism.

10.1. The specificity of early brain overgrowth as an indicator of autism

There is no doubt that the use of a brain overgrowth index as an early warning sign for autism has substantial scientific and clinical potential. While there are many points to consider, one relates to the issue of specificity; do only infants who will later develop autism show this large change in brain growth over a short period of time?

The answer to this question is quite simply, no. First, in our recent report on HC changes during infancy in autism, we also reported that 6% of normal control infants showed large jumps in HC from near normal at birth to far beyond normal size during the first year of life (Courchesne et al., 2003). In our study, this longitudinal result was based on a small sample of normal infants ($n = 31$) from the Fels Longitudinal Study, and a much larger sample is needed to confirm this percent. Second, as discussed further below, other recognized medical disorders may also present with sudden and excessive increases in head size during infancy.

It is also important to make the distinction between absolute brain size, and rate of brain growth. A hypothetical "early brain overgrowth indicator" or "index" of autism could be defined as the *change* in head circumference between birth and 1–2 years of age. Our past MRI and head circumference research found that the great majority of infants who later developed Autistic Disorder had normal average or below normal HC at birth but then showed a jump in HC greater than 1.5 S.D.; in fact, over 50% showed a change greater than 2 S.D. between birth and 1–2 years of age. Thus, an infant who begins life with a much larger than normal HC measurement does not fit this pattern, but one who has a head size below normal for the first several months and then shows a jump to beyond the 80th or 90th percentile does.

While use of such a hypothetical indicator of excessive HC change during the first year or so of life would likely catch a large percentage of infants who will eventually develop autism, it would also incorrectly identify a significant percentage of normally developing infants (i.e., about 6%, as noted by Courchesne et al., 2003). At this point, then, the potential for a Type-1 error when using such an indicator in isolation is large. Recently, significant advances have also been made in identifying early behavioral indicators of possible autism (Wetherby et al., 2004), but like HC, when used in isolation, they too have significant shortcomings in terms of specificity and sensitivity. Interestingly, however, when used with infants, HC indicators might be too likely to err on the false positive side, while behavioral indicators might be too likely to err on the false negative side. Perhaps together, they may make an effective combination for clinical use in infants and young toddlers. We think it important for research to explore how the two can be used in combination to create a more sensitive and accurate warning signal alerting clinicians to pay closer attention to the infant's behavioral development. Future studies are also needed to establish the normal longitudinal changes in the rate of brain growth within large samples of healthy typically developing infants. Current HC norms may not be reflective of within-infant growth patterns. Information on the rate of change (e.g., sudden and abnormal acceleration in size) can only be obtained from longitudinal studies of head growth in large samples. Such studies are currently underway in our laboratory.

There are also several recognized medical disorders that present with excessive head size in infancy. However, clear clinical differences distinguish autism from other disorders involving macrencephaly (see Table 1). Also, among these medically recognized disorders that may present with macrencephaly during infancy, Autistic Disorder is the most common, occurring once in every 500 infants and autism spectrum disorders (which includes Autistic Disorder) occur once in every 160 infants (Fombonne, 2002). By comparison, the majority of the other disorders are rather uncommon, and many are very rare, such as M-CMTC syndrome for which only 30 cases have been reported worldwide (Table 1).

As summarized in Table 1, a variety of neuroanatomical, physical, metabolic, behavioral and/or other clinical characteristics distinguish other disorders from autism. For example, autism does not typically involve pronounced ventricular enlargement, but this is a common feature of several other disorders presenting with excessive head size during infancy such as Sotos syndrome, hydrocephaly, and M-CMTC. Similarly, autism does not present with craniofacial abnormalities that are commonly present in other disorders; for example, children with Sotos syndrome often have an enlarged forehead and receding hairline, and children with Cowden syndrome may have tumors or cobblestone like papules on the face and body.

Additionally, while it is unlikely for autism to involve excessive head enlargement in utero because newborns with the disorder are typically born with normal to smaller than normal head size, some disorders do present with macrencephaly in utero. For example, Chen et al. (2002) reported that a child with Sotos syndrome had a head circumference that exceeded the 97th percentile during an

Table 1
A selected list of other syndromes characterized by early brain overgrowth

Syndrome	Age of observed macrocephaly	Neurobiological profile	Behavioral and cognitive profile	Physical characteristics	Genetic association	Incidence
Sotos syndrome (''cerebral gigantism'')	Birth (90% of cases (Cohen, 2002); in one case, macrocephaly evident by 31 weeks gestation (Chen et al., 2002)	Enlargement or other abnormality of cerebral ventricles (90%; Cohen, 2003); thinning of the corpus callosum (97%), particularly the posterior region and increased CSF spaces (79%; (Schaefer et al., 1997)	Neonatal hypotonia; early feeding difficulties; clumsiness and poor coordination; mild mental retardation to normal intelligence	Increased birth length and weight; advanced bone age; distinctive facial features such as prominent forehead, receding hairline, pointed jaw and ocular hypertelorism (increased distance between eyes; (Sotos et al., 1964)	Mutations in the NSD1 gene in majority of patients (Douglas et al., 2003; Rio et al., 2003)	Over 300 reported cases (Cohen, 2002). Estimated prevalence 1 in 10,000 to 1 in 50,000 (Sotos, 1997)
Canavan disease	Age of onset inconsistent among patients; macrocephaly occasionally observed at birth, but may not be noted until several months later, sometimes not until 1 year (Traeger and Rapin, 1998)	A degenerative disease causing deterioration of white matter. Death usually occurs within the first few years of life (Gordon, 2001)	Severe psychomotor handicaps present soon after birth; muscular hypotonia and a general failure of cognitive and motor development (Gordon, 2001)	Affected children secrete large amounts of N-acetylaspartic acid in their urine (Matalon et al., 1988)	Mutations in the gene for aspartoacylase l ocated on chromosome 17; an autosomal recessive mode of inheritance (Sistermans et al., 2000)	Rare in the general population, but more common in Ashkenazi Jews (carrier rate 1 in 40) (Sistermans et al., 2000)
Simpson-Golabi-Behmel syndrome (SGBS)	Pre and postnatal macrocephaly	Syndrome only seen in males (although females can have partial expression) with a high rate of neonatal death	Hypotonia; typically normal intelligence (Neri et al., 1998)	Increased birth weight and length; congenital heart defects, supernumerary nipples; coarse face (Lin et al., 1999)	X-linked syndrome; Glypican 3 (GPC3) mutations (deletions) in some patients (Li et al., 2001)	
Neurofibromatosis, Type 1	Macrocephaly in majority but not all patients, (Cutting et al., 2000; North, 2000)	Lesions (referred to as regional signal hyperintensities) in majority of patients (Cutting et al., 2000; North, 2000). Hyperintensities are observable on MRI T2-weighted images and may represent foci of neural dysplasia or dysmyelination (DiPaolo et al., 1995). Benign and malignant tumors (Arun and Gutmann, 2004)	Learning disabilities in majority (North et al., 1997) including a high incidence of ADHD (Arun and Gutmann, 2004)	Predominantly pigmentary abnormalities including café-au-lait macules, skinfold freckling and iris hamartomas (Arun and Gutmann, 2004)	Mutation in the NF-1 gene; autosomal dominant transmission; equally prevalent in males and females (North, 2000)	1 in 3000 (Arun and Gutmann, 2004)
Cowden syndrome	Macrocephaly in about 39% (Hanssen and Fryns, 1995) to 85% (Starink et al., 1986).	Seizures	Mild to moderate mental retardation delay of motor development (Hanssen and Fryns, 1995)	Multiple neoplasms (tumors), both benign and malignant, of the skin, breast, thyroid and gastrointestinal tract; lesions of the face and limbs; cobblestone like papules on face and body (Goffin et al., 2001)	Mutations in PTEN gene (a tumor suppressor gene) in q22–q23 region of chromosome 10; genetically transmitted cancer syndrome; inherited in an autosomal dominant pattern (Nelen et al., 1996).	
Weaver syndrome (WS)	Macrocephaly	Wide range of abnormalities noted, although not consistently, including cysts on the septum, dilation of ventricles and hypervascularization (Ardinger et al., 1986; Cohen, 1999)		Macrosomy, advanced skeletal age. Low pitched and horse cry (Cohen, 2003)	Genetic links currently unknown. However, WS found in multiple family members, suggesting an autosomal dominant pattern of inheritance in some cases (Proud et al., 1998). Some evidence of NSDI mutation like Sotos, but only in a small percentage (Douglas et al., 2003)	Rare; approximately 30 cases reported

ultrasound exam at 31 weeks gestation. For those disorders that routinely present with macrocephaly at birth (e.g., Sotos, SGBS, M-CMTC and Perlman), it must be the case that, unlike autism, excessive head size was achieved prenatally.

10.2. Severity of early brain overgrowth may predict later clinical outcome

As briefly noted above, we recently found that the magnitude of brain overgrowth in the first year of life was predictive of clinical behavioral outcome 5 or 6 years later (Courchesne et al., 2003). Specifically, within the autism spectrum disorder (ASD) sample, the HC increase from birth to 11 months was greatest in those infants with the more severe clinical outcome, namely Autistic Disorder (+2.2 S.D. jump), and least in those with the relatively milder outcome, namely, PDD-NOS (+0.6 S.D. jump). Every AD infant had a jump greater than every PDD-NOS infant. This surprisingly strong relationship between magnitude of brain development defect and degree of subsequent clinical impairment is important to replicate since it has strong diagnostic, prognostic, and brain-behavior explanatory significance. If, as suggested in the above discussion, the explanations for the early signs of autistic behavior reside in the neural defects preceding or immediately underlying brain overgrowth, then the magnitude of early brain overgrowth should become a good and perhaps clinically helpful index of diagnostic and prognostic decision-making. The possibilities as well as problems involved in establishing such an ''early brain overgrowth index'' remain to be solved, as pointed out above.

11. Conclusions and future directions

Autism is neither a subtle behavioral disorder nor the result of a single or mild form of neuronal abnormality. Autism involves widespread neuronal maldevelopment, with some structures far more affected (e.g., frontal lobes, cerebellum) and others much less affected (e.g., occipital cortex). If our hypothesis is correct, then maldevelopment of large pyramidal neurons such as spindle neurons or large inhibitory neurons such as chandelier cells would be just two examples among many neuronal and circuitry defects in frontal cortex, and these in turn would be a subset of all cerebral, cerebellar and limbic developmental defects in the autistic brain.

Maldevelopment on this scale, therefore, very likely reflects substantial defects ranging from neuronal numbers to molecular function and local and long-distance connectivity. The recognition of this process as *ongoing* and massive reminds that autism is indeed a disorder of the develop*ing* brain. In the developing brain, the neural structural and functional landscape is created where none existed before, and so when aspects of this process go substantially awry, as in autism, we should expect to see a differently detailed landscape (connectivity, molecular expression, etc.) and not simply a largely normal landscape with perhaps just one or two specific features precisely and conveniently omitted or changed.

We further hypothesize that a pivotal change in the autistic neural landscape is maldevelopment of large frontal pyramidal cells and interneurons that together normally provide two indispensable functions: integrating diverse information from widespread systems, and providing temporally coherent and essential context-based control and corrective input to those systems.

It now seems possible that neurobiological findings in autism, such as abnormally accelerated brain growth, could begin to intersect with early diagnosis efforts. While clinical tools such as the ADOS (Lord et al., 1998) and CHAT (Baron-Cohen et al., 1992), give practitioners more certainty in making preliminary diagnostic decisions about a child suspected of having autism as early as 18 months of age; it is an exceptional case that begins treatment at that time. Our finding of abnormal early brain growth in autism will hopefully be used as a scaffold for the development of biological and behavioral instruments that can be used at an infant's 12-month well baby check-up.

The precise nature and format of such bio-behavioral diagnostic tests are currently undetermined. Retrospective videotape analyses of 12 months or younger, however, may provide clues. Studies have identified three general domains of behavioral abnormality that are present on or before the first birthday in children who will later develop clear signs of autism; namely, social responsiveness, attention and motor behavior (Maestro et al., 2002; Osterling and Dawson, 1994; Teitelbaum et al., 1998). For example, according to Maestro et al. (2002), by the time an infant is 6 months old, he/she displays abnormalities in social attention behaviors that can potentially signal autism. They found that infants later diagnosed as autistic spent less time looking at people and orienting towards people than normally developing infants. Deficits in social and attention behaviors, however, are often difficult to ascertain, especially when such abnormalities are subtle. While such findings hold considerable theoretical value, it is unlikely that indices of social attention behaviors alone could be used to make a definitive diagnosis of autism during the first months of life. In combination with HC measures, however, the predictive value of such a measurement will likely be improved.

At this stage, the potential of studies of HC and brain growth for broadening our scientific knowledge of the underlying biological pathology of autism may supercede the immediate diagnostic power associated with the phenomenon of accelerated early brain growth in autism (Lainhart, 2003). One example comes from a new postmortem study that raises possible links with early brain overgrowth and arrest of growth on the one side, and previous theories and animal models of neuroinflammatory responses on the other. This new postmortem study of autism

that reports evidence of an on-going neuroinflammatory reaction in patients that may play a pathogenic role (Vargas et al., 2005). That study found evidence of an active neuroinflammatory process in dorsal frontal cortex, cingulate cortex, and cerebellum; the response included microglial and astroglial activation. Abnormality was especially prominent in cerebellar white matter. In the cerebrum, abnormality occurred in white matter underlying cortex; frontal and cerebellar cortical involvement were also demonstrated. Thus, the regions that showed the greatest active neuroinflammatory responses, are also the ones showing the greatest early developmental overgrowth and arrest of growth reported in MRI studies. For example, in the first study to report white matter developmental abnormality in autism (Courchesne et al., 2001), abnormality was also most prominent in cerebellar white matter, and in the first studies of cerebral white matter abnormality in autism (Carper et al., 2002), the lobe with the greatest white matter enlargement was the frontal lobe. Finally, in the first studies to examine subregional white matter effects, the most deviant was white matter immediately underlying cortex (Herbert et al., 2004) especially frontal cortex (Herbert et al., 2004) including cingulate (Barnea-Goraly et al., 2004).

Thus, a surprising possibility arises that warrants further experimentation: Does abnormal early brain enlargement and subsequent slowed or arrested growth reflect an active neuroinflammatory process? Does a neuroinflammatory-related increase in neuroglial numbers and size during late prenatal or early postnatal life underlie the early brain overgrowth? Does the slow or arrested growth in brain size by early childhood reflect the point at which the neuroinflammatory response and neuroglia activation in numbers and size reach a maximum? If the type of reported neuroinflammatory response and neuroglial activation does underlie the abnormally accelerated HC growth in the first year of life, it must begin in prenatal or perinatal life. If so, then it becomes a reasonable hypothesis that the described type of inflammatory response or the processes that trigger it might be involved in disrupting one or more of several late neurodevelopmental processes including cell migration, axon targeting and elimination, apoptosis, neuronal differentiation, dendrite outgrowth and synaptogenesis, and minicolumn growth and functional differentiation. Immunological responses have long been suggested to play a role in brain maldevelopment in autism (Patterson, 2002), and animal models of immunological activation have been created that have normencephaly at birth but macrencephaly by adulthood, reduced pyramidal neuron size, increased neuron density, and abnormal social and non-social behaviors that appeared to be ‘‘autistic-like’’ (Fatemi et al., 2002; Shi et al., 2003; Patterson, 2002). Whether there may be a connection between these previous theories and models and the innate neuroinflammatory response observed by Vargas and colleagues, remains to be determined.

Other issues await further exploration and discovery, including other mechanisms that might trigger and control the type of early brain growth we have described, the degree of universality of abnormal early brain growth in autism, and the development of new animal models that take this neurophenotype into account, as well as the histology and molecular biology of early brain tissue, to name a few. The future of both clinical and scientific practice will undoubtedly move to meet these new challenges.

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