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Research Report

Brain growth across the life span in autism: Age-specific changes in anatomical pathology

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ABSTRACT

Autism is marked by overgrowth of the brain at the earliest ages but not at older ages when decreases in structural volumes and neuron numbers are observed instead. This has led to the theory of age-specific anatomic abnormalities in autism. Here we report age-related changes in brain size in autistic and typical subjects from 12 months to 50 years of age based on analyses of 586 longitudinal and cross-sectional MRI scans. This dataset is several times larger than the largest autism study to date. Results demonstrate early brain overgrowth during infancy and the toddler years in autistic boys and girls, followed by an accelerated rate of decline in size and perhaps degeneration from adolescence to late middle age in this disorder. We theorize that underlying these age-specific changes in anatomic abnormalities in autism, there may also be age-specific changes in gene expression, molecular, synaptic, cellular, and circuit abnormalities. A peak age for detecting and studying the earliest fundamental biological underpinnings of autism is prenatal life and the first three postnatal years. Studies of the older autistic brain may not address original causes but are essential to discovering how best to help the older aging autistic person. Lastly, the theory of age-specific anatomic abnormalities in autism has broad implications for a wide range of work on the disorder including the design, validation, and interpretation of animal model, lymphocyte gene expression, brain gene expression, and genotype/CNV-anatomic phenotype studies.

1. Introduction

Recent research has led to the theory of age-specific anatomic abnormalities in autism (Courchesne et al., 2001, 2007; Courchesne and Pierce, 2005) (see Fig. 1). At early ages, there is abnormal overgrowth of the brain in autism, but during adolescence and young adulthood, there may be abnormal decline and possible degeneration (Fig. 1). Because early abnormal overgrowth occurs at the time of the first detectable behavioral and clinical signs of autism (Pierce et al. 2009; Pierce, in review) (Table 1), neural defects that cause overgrowth may be the neural bases of autism.

This theory was originally based on evidence from four studies in the early 2000s. First, in an MRI study, Courchesne et al. (2001) reported evidence of an unusual brain growth trajectory in autism. They discovered abnormal brain and cerebrum enlargement in autistic 2- to 4-year olds, but also observed slightly smaller overall brain volumes in autistic 12 to 16 year olds (Fig. 2). Subsequent studies also reported brain or cerebral overgrowth in autistic 2- to 4-year olds (Carper et al.

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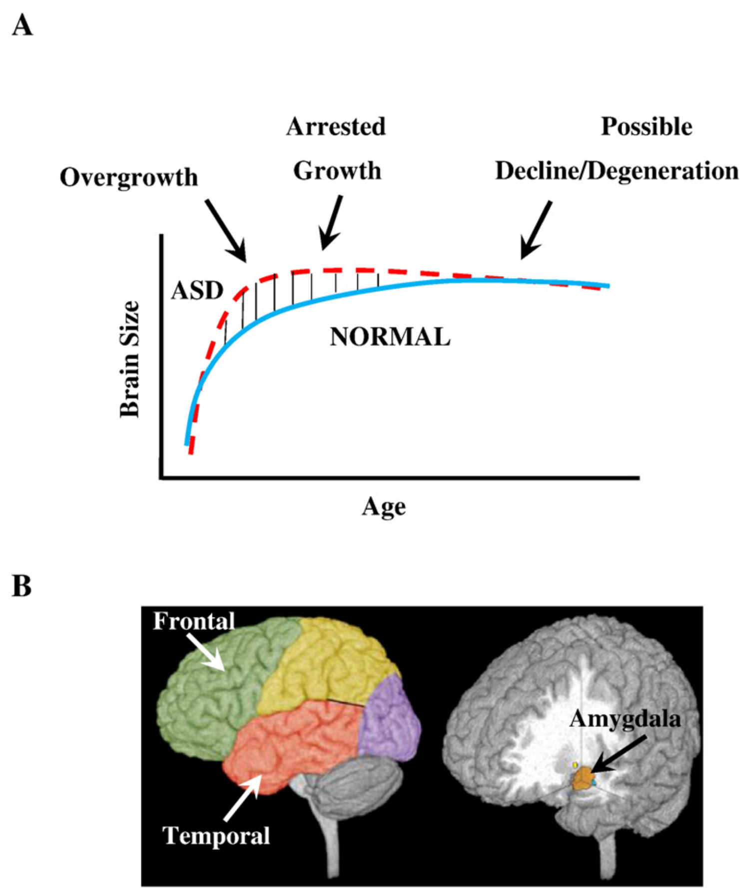

Fig. 1 – Three phases of growth pathology in autism. (A) Model of early brain overgrowth in autism that is followed by arrest of growth. Red line represents ASD, while blue line represents age-matched typically developing individuals. In some regions and individuals, the arrest of growth may be followed by degeneration, indicated by the red dashes that slope slightly downward. (B) Sites of regional overgrowth in ASD include frontal and temporal cortices and amygdala (from Courchesne et al., 2007).

2002; Sparks et al., 2002; Hazlett et al., 2005; Bloss and Courchesne 2007; Schumann et al. 2010), while autistic adolescents and adults have been reported to display cortical atrophy (Hadjikhani et al., 2006) and reduction in amaygdala (Aylward et al., 1999; Pierce et al., 2004) and frontal cortex volumes (Kosaka et al., 2010) (reviews: Amaral et al., 2008; Courchesne et al., in press). Moreover, meta-analyses of MRI brain volume in the autism literature (Redcay and Courchesne, 2005; Stanfield et al., 2008) and postmortem autistic brain weight (Redcay and Courchesne, 2005) also confirm early brain overgrowth in autism by 2 to 6 years of age.

Table 1 – Red flags of autism spectrum disorder by 1 to 2 years of age.

Reduced social interest and affect
Lack of warm, joyful emotional expressions
Lack of sharing emotional enjoyment or interest
Lack of response to name
Lack of showing and interacting
Abnormal language development
Lack of coordination of gaze, facial expression, gesture, and sound during interactions

Second, based on analyses of head circumference (HC), it was discovered that this abnormal brain enlargement is not present at birth in most cases but instead begins during the

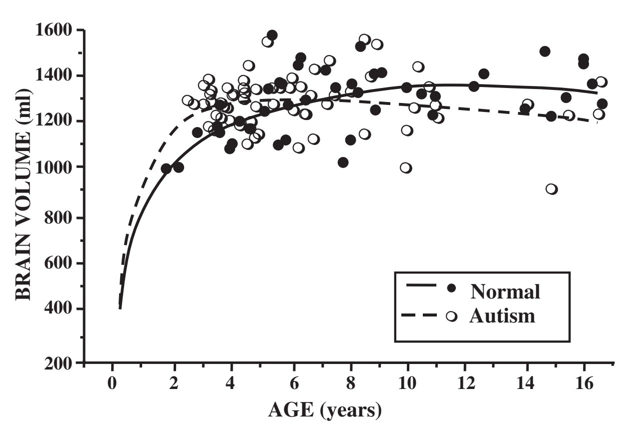

Fig. 2 – Brain growth in autism through 16 years. Data plot shows larger MRI-based volumes in autistic 2- to 4-year-old males as compared to normal 2- to 4-year-old males and smaller overall brain volumes in autistic 8–16 year olds as compared to normal (from Courchesne et al. 2001).

first 2 years of postnatal life (Courchesne et al., 2003). Multiple HC studies since then have also found early pathological HC overgrowth in the first postnatal years (Hazlett et al., 2005, Dementieva et al., 2005, Dissanayke et al., 2006, Dawson et al., 2007, Mraz et al., 2007, Webb et al., 2007, Elder et al., 2008; Fukumoto et al., 2008).

Third, Carper et al (2002) determined that this overgrowth had an important gradient in the cerebrum: greatest in frontal and temporal cortices and least in occipital (Fig. 3). This finding has also been reported in subsequent studies (Schumann et al., 2010; reviews: Courchesne et al., 2007, in press) (Fig. 3).

Finally, Dawson and colleagues (Sparks et al., 2002) discovered overgrowth of the amygdala, a structure vital to emotional processing and memory, in autistic 4-year olds. Subsequent studies have verified and extended these findings showing associations between degree of overgrowth and severity of clinical symptoms (Munson et al., 2006, Mosconi et al., 2009, Schumann et al., 2009). The underlying neural defects that cause overgrowth in frontal and temporal cortices and the amygdala have yet to be identified. Whatever these underlying early defects may be, they will likely explain why autistic behavior develops and provide clues as to the genetic or non-genetic factors that trigger those overgrowth defects.

Thus, many MRI studies have found abnormal early overgrowth in several regions that mediate the development of higher order social, emotion, language, and communication abilities, namely, frontal and temporal cortices and the amygdala (reviews: Courchesne et al., 2007, Amaral et al., 2008; Courchesne et al., in press). Nonetheless, how anatomic pathology alters with age after these early years is little studied. To gain insight into this question, two studies (Redcay and Courchesne, 2005; Stanfield et al., 2008) conducted formal statistical meta-analyses of a large number of separate reports, each of which represented a different relatively narrow age window. Both meta-analyses showed statistical evidence suggestive of substantial age-related changes in the degree of deviation from normal in brain size in autism.

However, as recently pointed out (Courchesne et al., in press), no single study has ever directly examined age-related changes across early life to adulthood in autism because of the difficulty in collecting MRI scans across such a wide age range in autistic and healthy typical subjects. Without direct evidence, age-related differences in pathology at younger versus older ages remain no more than a statistical inference from these meta-analyses.

Here, in the largest autism MRI sample ever analyzed, we report in 2- to 50-year olds the first direct longitudinal and cross-sectional MRI evidence in support of the theory of age-specific anatomical abnormality in autism. We found strikingly different pathological trajectories in brain size during early as compared to later life in autism, with overgrowth evident in early life but an accelerated rate of decline marking adult life.

2. Results

Growth curves of overall brain size across the life span from 2 to 50 years of age in ASD are shown in Fig. 4. The growth curves reveal an early period of brain overgrowth in ASD boys and girls followed by slowed growth during later childhood when the normal brain catches up with that of the autistic brain volumes. Thereafter, brain volumes decrease in size in ASD at a faster rate than normal so that, in ASD males, by later adulthood, the brain is slightly smaller than average.

This very large sample, longitudinal and cross-sectional MRI study of male and female brain size in autism across the life span from 2 to 50 years strongly supports the theory of age-specific anatomic abnormalities in autism. The results show that there are at least three different periods of pathological

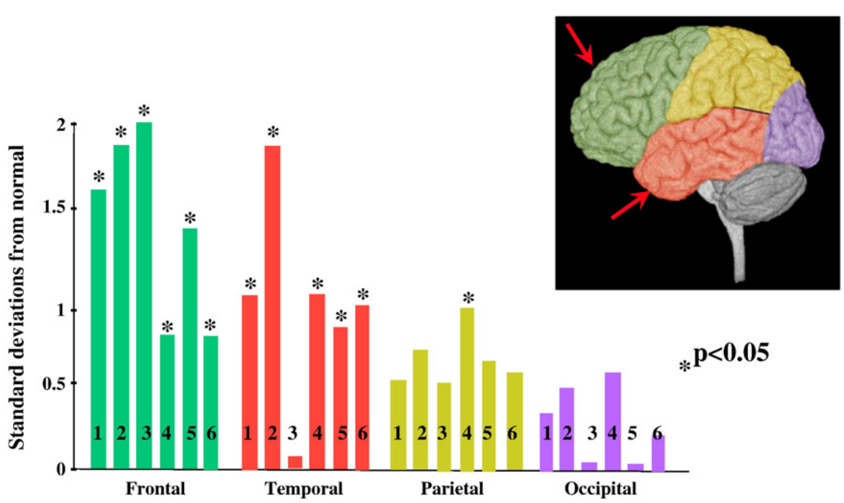

Fig. 3 – Gray matter overgrowth in autism. The bars represent abnormalities in different cerebral regions (standard deviations from normal average) in children and adolescents with ASD. Note the general gradient of abnormality with frontal and temporal regions most abnormally enlarged. Asterisks indicate statistically significant differences ($p < 0.05$) in autism as compared to normal control. References: (1) Carper et al., 2002, 3.4 years; (2) Bloss and Courchesne, 2007, 3.8 years; (3) Kates et al., 2004, 7.6 years; (4) Palmen et al., 2005, 11.1 years; (5) Hazlett et al., 2006, 19.1 years; (6) Schumann et al., 2010, 2–4 years (from Courchesne et al, 2007).

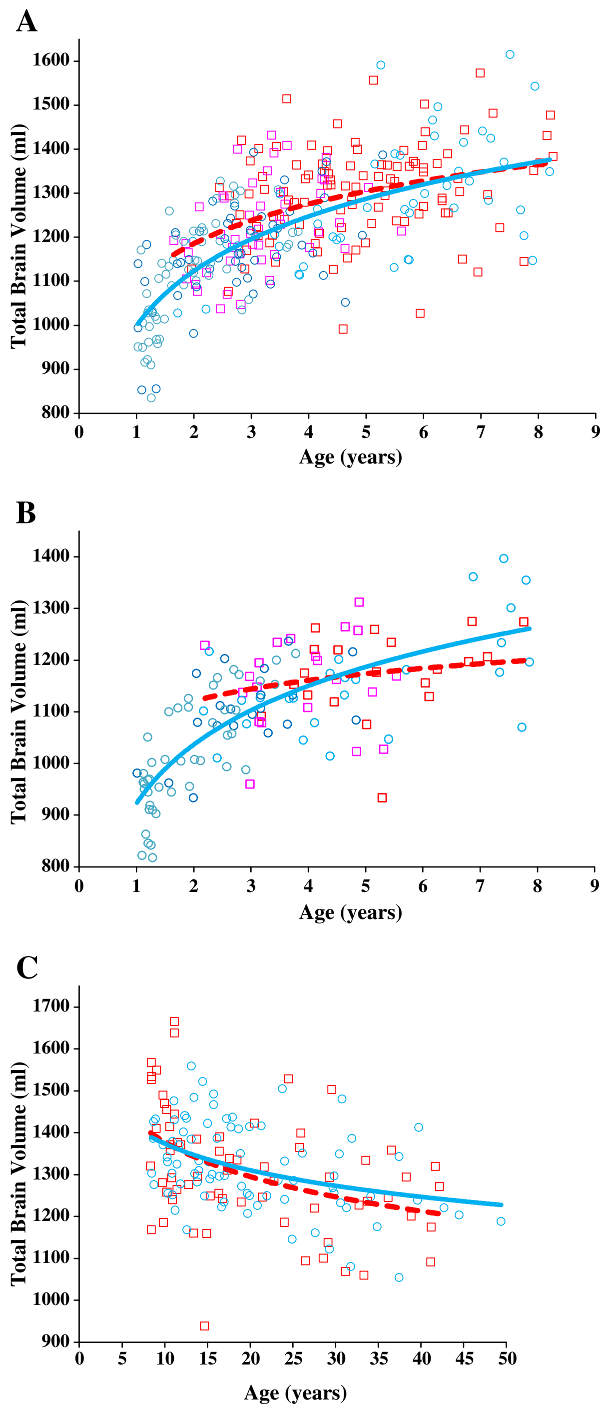

Fig. 4 – Changes in brain size across the lifespan in ASD. Total brain volume is shown for ASD (squares) and control (circles) subjects for (A) males aged 1 to 9 years, (B) females aged 1 to 9 years, and (C) males aged 9 to 50 years. Different colored markers represent the 3 different source datasets. The red, dotted lines represent growth normal trajectories of ASD subjects. The blue solid lines represent the growth trajectories of normal control subjects.

brain development in ASD. Early in postnatal life in autism, there is a relatively brief period lasting several years or less marked by abnormally accelerated brain overgrowth. This short period is followed by a period of abnormally slowed or arrested growth between young childhood and older childhood or preadolescence. This second short developmental period of growth pathology has been most carefully examined by Carper et al. (2002), who showed strikingly reduced growth changes in autism between 2–4 years of age and about 9 years of age in frontal and temporal cortical regions, as compared to typical children whose growth in those regions remained steady and robust (see Table 2). Next, our life span evidence in Fig. 4 shows what may be a premature and accelerated rate of decline in brain size from adolescence to later middle age in autism.

3. Discussion

The genetic, molecular, and cellular pathologies in autism that create the sudden and accelerated overgrowth during the first years of life must begin before that early age period, namely during either prenatal or very early postnatal life. We theorize that the abnormally accelerated rate of early growth and then premature arrest of growth in the autistic brain signal innate abnormalities of initial cortical neural and laminar organization and connectivity that are not the result of experience and learning-based activity. By contrast, the normal child's brain grows more slowly, likely reflecting continued refinement of organization and connectivity via adaptive functional activity guided by experience and learning; indeed, some MRI-behavior studies of normal development indicate that slower growth, especially in frontal lobes, is associated with a higher ability long-term outcome (Shaw et al., 2006).

Since the first description of the unusual brain growth trajectory in autism, it has been theorized that the overgrowth might be due to excess neurons consequent to cell cycle dysregulation and/or failure of naturally occurring apoptosis (Courchesne et al., 2001; Courchesne et al., 2007). To test that possibility, we chose to quantify neuron counts, using stereological methods, in one of the regions with pathological early overgrowth, namely frontal cortex. In a pilot study, we found that a 3-year-old autistic postmortem male had 43% more neurons in dorsolateral prefrontal cortex as compared to a 2-year-old control male. In ongoing work, our laboratory has found this excess of neuron number in dorsolateral prefrontal cortex in every young autistic male we have analyzed to date. There is no known neurobiological mechanism in humans capable of generating during postnatal life the large excesses of frontal cortical neuron numbers we are

Table 2 – After early overgrowth in autism, there is abnormally slow or arrested growth (from Carper et al., 2002).

	%Increase in volumes during childhood		
	Normal	Autism	
Frontal gray	20%	1%	from 2–4 to 6–8 years
Frontal white	45%	13%	from 2–4 to 7–11 years
Dorsolateral prefrontal gray	48%	10%	from 2 to 9 years
Temporal gray	17%	0%	from 2–4 to 6–8 years
Temporal white	22%	2%	from 2–4 to 7–11 years

finding. The great magnitude of this excess can only be due to abnormal events and processes beginning in prenatal life and cannot be due to any known postnatal event or mechanism. With the exception of newly discovered cortical laminar abnormalities in some autistic cases (Courchesne and colleagues, in progress), there are no other prenatal biological defects that are known to occur in the majority of young autistic cases (see reviews by Amaral et al., 2008; Courchesne et al., in press; Wegiel et al., 2010). Therefore, this prenatally based excess of neuron numbers, if verified by analyses of still further young autistic cases by us and other researchers, would be the earliest known indicator of the original biological events that cause autism.

Overgrowth and excessive neuron numbers and aberrant patterns of connectivity and functional activity could eventually trigger a belated "corrective" or remodeling phase involving processes that attempt to prune the excess aberrant axon connections, synapses, and neurons to improve neural circuit function. Evidence of neuroinflammatory processes in the autistic person may reflect such secondary remodeling processes (Morgan et al., 2010). The life span evidence in the present study (Fig. 4) plus a large existent literature points to such secondary, possibly degenerative, changes. Indeed, evidence from over 200 MRI, DTI, and postmortem studies of the adolescent and adult autistic brain (reviews: Amaral et al., 2008; Courchesne et al., in press; Murphy et al., in press) collectively paint a picture of degeneration, atrophy, neuron loss, reduction in size of specific structures, and neuroinflammation at that later age. Examples of such evidence in adolescents and young adults appear in Table 3 and include reduced neuron numbers in the amygdala and cortex, reduced minicolumn size, decreased dendritic arbors, cortical thinning and atrophy, abnormally increased CSF volumes, activated microglia, increased pro-apoptotic and pro-neuroinflammatory signals. These defects at older ages in autism stand in contrast to the very young autistic brain: increased cortical neuron numbers, normal minicolumn size, and abnormally increased cortical and amygdala volumes.

Table 3 – Third phase of pathological brain development in autism: evidence of neuron loss and reduced size of anatomical structures in pre-adolescence to adulthood.

Decreased
- Amygdala neuron numbers (Schumann and Amaral, 2006)
- Amygdala volume (Pierce et al., 2004; Aylward et al., 1999)
- Fusiform gyrus neuron numbers (Van Kooten et al., 2008)
- Purkinje neuron numbers (Bailey et al., 2008; review Amaral et al., 2008)
- Neuron size in cerebrum and cerebellum (Kemper & Bauman, 1998; Fatemi et al., 2002; Casanova et al. 2006)
- Dendritic arbors (Martin-Ruiz et al., 2004)
- Minicolumn size (Casanova et al., 2002, 2006; Buxhoeveden et al., 2006; Morgan et al. 2008)
- Inferior frontal and insula volumes (Kosaka et al., 2010)

Thinning
- Cortical regions (Courchesne et al., 1993; Hadjikhani et al., 2006) (but some report thicker cortex: Bailey et al., 1998; Hardan et al., 2006)
- Corpus callosum (Egaas et al., 1995, review: Courchesne et al., in press
- Increased CSF (Hallahan et al., 2009)

Activated microglia and possible inflammation
- Increases in some pro-apoptotic, decreases in anti-apoptotic molecules (Araghi-Niknam and Fatemi, 2003)
- Microglia activation, pro- and anti-inflammatory molecules (Vargas et al., 2005, Morgan et al., 2010)

The anatomic pathology of autism changes with age. The changes are almost certainly continuous from prenatal life to old age, but rates and types of change will likely vary with brain region. Moreover, at different ages, there will likely be age-specific defects (e.g., overgrowth of amygdala, temporal and frontal cortex, and brain at young ages but not at older ages); that is, defects present at younger ages may not be present at older ages and conversely. Nonetheless, potentially some subset of core and early generative neural defects may be detectable across a wide age range, perhaps even across a lifetime. In general, however, we hypothesize that age-related change will mark gene expression, molecular features, synaptic composition, cellular characteristics, circuit patterns, and macroscopic morphology. Gene expression abnormalities in the adolescent and adult autistic brain will not be the same as those in the prenatal or toddler autistic brain. Gene expression in static, development-neutral preparations such as lymphocyte lines may not bear complete fidelity with the actual gene expression profiles in the living, developing, and changing infant, toddler, child, adolescent, or adult autistic person. The same would apply to identification of brain protein, synaptic, minicolumn, neuron count, or other defects in the adult autistic brain. Whether a defect at that older age is an age-specific one or a core defect that is continuously present since early development would be difficult if not impossible to determine in the absence of verification in the very young brain.

This principle of age-specific change in pathology also applies to the cerebellum in autism, even though its trajectory of growth pathology seems to differ from that of the cerebrum and amygdala (Webb et al., 2009; Hallahan et al. 2009; reviews: Stanfield et al., 2008; Courchesne et al., in press). Subregions of the cerebellar vermis show varying degrees of abnormality with the most consistent one, vermis lobules VI–VII, showing hypoplasia by 10 months of age and throughout infancy, childhood, and adulthood (Fig. 5). The cerebellar hemispheres also display complex change with age, being near normal in size at young ages to reduced in size by adulthood (Fig. 5) (review: Courchesne et al., in press). Purkinje neuron loss in the cerebellum was not reported for the youngest autistic child examined in one study (Bailey et al., 1998) but was present in every autistic adult in that study.

There is currently much interest in brain-gene mapping, but this effort will necessarily run headlong into the problem of age-specific brain effects. Therefore, brain-SNP, brain-CNV (copy number variation), or brain-"deep phenotype" studies of older children, adolescents, and adults with autism will be prone to reflect outcome associations and not original causal ones. In general, discovery of the causes of autism will be more difficult via studies of the older as compared to the very young autistic brain. Inferences about causes and early processes derived from data on older cases should be made with caution.

On the other hand, the importance of studies of the adolescent, adult, and aging autistic brain is very high, but for reasons having less to do with the search for original early

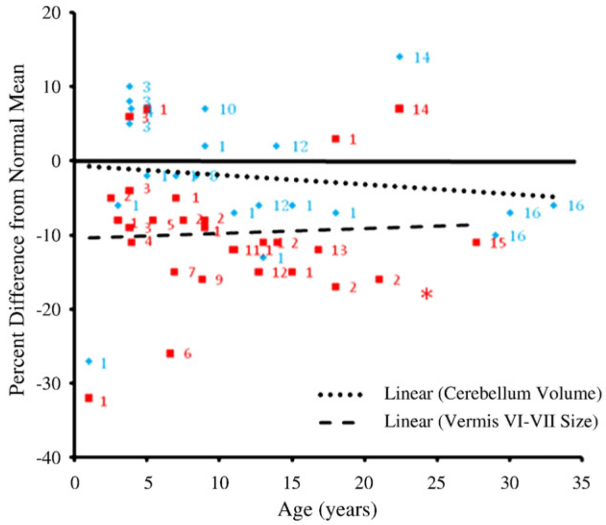

Fig. 5 – Cerebellum and vermis size from infancy to adulthood in autism. Percent differences from normal average in each study of autistic subjects are plotted for cerebellar volume (blue diamonds) and vermis lobules VI–VII cross-sectional area (red squares) against age. Regression lines are shown for cerebellar volume and vermis lobules VI–VII area. The solid line represents normal average. Each number represents a separate study: (1) Hashimoto et al., 1995; (2) Courchesne et al., 2001; (3) Akshoomoff et al., 2004; (4) Webb et al., 2009; (5) Carper et al., 2000; 6, Kleiman et al., 1992; (7) Kaufmann et al., 2003; (8) Kates et al., 2004; (9) Mitchell et al., 2009; (10) Herbert et al., 2003; (11) Elia et al., 2000; (12) Cleavinger et al., 2008; (13) Ciesielski et al., 1997; (14) Hardan et al., 2001; (15) Piven et al., 1992; (16) Hallahan et al., 2009. Data point from first report of hypoplasia of vermis lobules VI–VII (Courchesne et al., 1988) shown as red asterisk.

developmental causes and defects. Instead, as delineated by a companion paper in this Special Issue (Murphy et al.), studies of the older, including aging, autistic brain are vital because there are presently no proven methods for successfully improving clinical symptoms and neural functioning at these ages. Since the autistic brain is continuously changing in abnormal ways even across these older ages, as demonstrated by Murphy and colleagues (Raznahan et al. 2010), there may be ample opportunity to intervene pharmacologically as well as behaviorally to improve the very long term clinical course. In recent publications (Raznahan et al., 2010, Ecker et al., 2010), the ratio of cerebral lobar volume to overall total brain volume follows an abnormal trajectory across adolescence and adulthood, suggesting that in autism, abnormal neural and molecular processes continue to occur during adulthood. Murphy also reports that greater symptom severity is correlated with greater deviation from normal brain maturation (Ecker et al., 2010). Therefore, studying the autistic adolescent and adult brain could be important in guiding treatment throughout later life. This realization should re-invigorate research focused on understanding age-specific neural pathologies in the older autistic brain.

In conclusion, across the life span, autism displays complex age-specific anatomic changes, and underlying these changes must necessarily be age-related and potentially age-specific changes in gene expression, molecular, synaptic, cellular, and circuit abnormalities. A peak age for detecting and studying the earliest fundamental biological underpinnings of autism would be prenatal life and the first 3 postnatal years. This theory of age-specific anatomic abnormalities in autism has significant broad implications for a wide range of work on the disorder including the design, validation, and interpretation of animal model; lymphocyte gene expression; brain gene expression; and genotype/CNV-anatomic phenotype studies. Lastly, the search for signals of original, prenatal, and early postnatal causal defects is massively complicated, but not nullified, by this principle.

4. Experimental procedures

To further test the theory of age-specific anatomic abnormalities in autism, we analyzed 586 longitudinal and cross-sectional MRI scans from $N = 259$ ASD subjects ages 2 to 50 years and $N = 327$ typical subjects ages 1 to 50 years. This is many times larger than any previous MRI autism dataset and incorporates longitudinal MRI evidence from both young as well as much older autism and typically developing subjects. This large dataset encompasses MRI scans from our studies conducted across the past 18 years. This unique sample enabled us to analyze changes in the autistic brain across much of the life span up to late middle age. Evidence from about one-third of these scans has been reported in a series of publications (Courchesne et al., 2001, 2003; Carper and Courchesne 2000, 2005; Carper et al., 2002; Schumann et al., 2009, 2010). Longitudinal scans were collected from the majority of subjects, with shorter longitudinal intervals for younger subjects and longer ones for older subjects. Only a subset of the longitudinal scan data has been reported (Schumann et al., 2010). Data from 253 of these 586 total scans have not been previously reported by us. These 253 scans include 67 autistic and 83 typical control 9- to 50-year olds, and 103 scans from 1- to 4-year old typically developing subjects. As described in previous publications from our laboratory, all ASD subjects underwent state-of-the-art deep clinical phenotyping including ADI-R, ADOS, cognitive, language, family and medical history, and chromosomal analyses for fragile-X. ASD as well as typical controls with confounding medical or family history (e.g., fragile-X or other chromosomal defects, pre- or postnatal exposure to drugs, toxins or pathogens, etc.) were excluded from analyses. Across our sample, less than % of ASD subjects were multiplex, the rest being simplex. Three different MRI scanners, imaging protocols, and anatomical measurement programs were used across time, although longitudinal collections within an individual subject were always with the same scanner, protocol, and measurement program.

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