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Structural MRI in autism: Findings and future directions ☆

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Abstract

Structural MRI studies of the brain in autism have yielded inconsistent results until recent years. Studies over the past decade have revealed several exciting new findings and have fostered novel hypotheses about the onset and etiology of this disorder. The most consistent MRI finding in autism is that the brain is enlarged. Studies have suggested that brain overgrowth may be most robust early in development, but increased brain volume has been observed throughout adolescence and early adult life. Retrospective head circumference studies have indicated that the onset of brain enlargement may occur during the latter part of the first year of life and does not appear to be present at birth. Recent studies of infant siblings of children with autism suggest that the onset of the core behavioral features of autism also occur during the latter part of the first year of life and may not be present by 6 months of age. The coincident timing of the onset of brain and behavioral abnormalities in autism suggests that these features may be related. Future longitudinal MRI studies of infant siblings of children with autism will help elucidate this relationship and potentially delineate the pathogenesis of this disorder. Additional findings from structural MRI studies of autism have begun to map patterns of brain overgrowth across cortical lobes and tissue types (gray and white matter). These studies are somewhat inconsistent, but suggest generalized overgrowth affecting both cortical gray and cortical white matter, as well as several subcortical structures. The diffuse network of regions affected has shifted research attention from hypotheses about specific regions and structures to more widespread mechanisms involving neural circuits and diffuse mechanisms at the neuronal level. These findings, their implications for our understanding of the pathogenesis of autism, and future directions for structural MRI studies of autism are discussed.

1. Introduction

While high resolution magnetic resonance imaging (MRI) studies of the brain in autism have been reported since the late 1980s, the contributions of this research have been limited until recent years. Advancements have been slowed by several shortcomings, including small sample sizes that cannot adequately account for the heterogeneity in autism, a lack of longitudinal data, and failures to account for factors associated with brain morphology that confound analyses, such as cognitive ability and gender. Recently, an increased number of MRI studies have addressed several of the limitations of previous research and have begun to highlight key neuroanatomical abnormalities in autism more consistently.

Current understanding of aberrant brain development in autism recognizes that while specific neural circuits may be important, the underlying pathophysiology of autism affects numerous brain regions and is not limited to a specific structure. Autism is now posited as a disorder characterized by disrupted connectivity across neural circuits, in which multiple networks throughout the brain are affected [1,2]. Consistent with this hypothesis, MRI studies show overall brain enlargement in autistic individuals, suggesting that new conceptualizations of underlying neurobiological mechanisms will be necessary. Insights from related disor-

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ders such as Fragile X Syndrome, where diffuse abnormalities in dendritic spine morphology have been observed [3], are shifting our attention from specific lesion-function hypotheses to analysis of more widespread mechanisms that make sense in the context of a neurodevelopmental disorder that has its origins in early brain development and continues throughout life. In this review, we examine the major contributions of MRI to understanding the neuroanatomical phenotype in autism, explore how findings may inform our understanding of the pathogenesis of autism, and suggest directions for future research.

2. Brain volume in autism

Kanner's original report [4] of 11 autistic children noted that, despite an absence of significant dysmorphology, a number of children did have abnormally large heads. This original description has been supported by several studies over the past decade reporting that macrocephaly (head circumference greater than the 98th percentile) occurs more commonly in autistic individuals than controls. Rates of macrocephaly average around 20% [5–10]. These findings suggest that brain volume, which is highly correlated with head circumference (particularly at very young ages) might also be enlarged in autistic individuals.

Piven et al. [11] first noted increased total brain volume on MRI in a group of adolescents and adults (12–29 years of age) with autism, compared to both typically developing and intelligence quotient (IQ) comparable controls. The authors replicated this finding in an independent sample [12], noting that total brain volume was significantly increased in adolescents and young adults, after taking into account overall height, gender, and IQ. In addition, the volume of brain tissue only, as well as cerebrospinal fluid (CSF) volume, was noted to be increased. Courchesne et al. [13] expanded on these results, reporting both white and gray matter cortical volume enlargement in autistic subjects 2–4 years of age, but not autistic subjects 4–16 years of age, compared to typically-developing controls. The authors suggested that enlargement occurred transiently at ages 2–4 years, followed by a relative decrease in brain volume. Further support for early brain enlargement was reported by Sparks et al. [14] who noted increased overall brain volume in a large sample of 3- to 4-year-olds with autism compared to both typically-developing and developmentally-delayed, non-autistic controls. Moreover, Aylward et al. [15] reported enlarged brain volume in a sample of high-functioning autistic subjects 8–12 years of age, but failed to find enlargement in those over 12 years of age. Together, these studies suggest that the brain is enlarged in autism and that enlargement may be most robust (and therefore more readily detectable) early in development (Table 1).

3. Onset of brain overgrowth

Although Courchesne et al. [13] made the important post hoc observation of enlargement confined to a 2- to 4-year-old subset of a sample of 2- to 16-year-olds with autism, the sample of 2-year-olds in that study was limited, including only 12 autistic and 2 typically-developing control children. Cody Hazlett et al. [16] recently reported cortical enlargement in a large sample of 2-year-olds with autism, suggesting that this phenomenon is present early in development. Estimates of the onset of brain enlargement have come from retrospective longitudinal studies of head circumference. In a retrospective chart review of autistic individuals with macrocephaly, Lainhart et al. [9] noted that macrocephaly typically was not present at birth. These observations were strengthened by retrospective findings in a larger sample by Stevenson et al. [10] showing the absence of macrocephaly at birth in 17 of 18 autistic individuals who later developed macrocephaly. Subsequently, Courchesne et al. [17] reported retrospective, longitudinal head circumference measurements in a sample of 15 autistic individuals with observations at 4 time points (on average) between birth and 14 months. This study found evidence of enlargement in head circumference, compared to published population norms, occurring in an age bin arbitrarily set at 6–14 months of age. Decreased head circumference was observed at birth in this sample. Combining these results with those from their 2001 MRI study [13], the authors hypothesized that brain size in autism is initially small, followed by a period of overgrowth, followed by a period of decelerated growth and relative volume loss.

More recently, Cody Hazlett et al. [16] reported a longitudinal retrospective investigation of head circumference in a large sample of autistic ($N = 113$) children and locally-ascertained community controls ($N = 189$) between birth and 3 years. This study accounted for a number of potentially confounding factors, such as social economic status, ethnicity, gender, and body size, and excluded subjects from both case and control groups who had evidence of significant perinatal adversity. Subjects had an average of 4 retrospective head circumference measurements between birth and age 3 years. The authors observed that head circumference was significantly enlarged in autistic individuals by age 3 and that enlargement had its onset at approximately 12 months of age (Fig. 1). Findings also suggested that head circumference did not differ between cases and controls at birth.

Since, the first biological theories of the pathogenesis of autism, this disorder generally has been assumed to have its beginnings during the prenatal period. Neuropathological studies by Bauman and Kemper [18] show densely packed immature neurons in the limbic structures of the brain and persistence of climbing fibers from the inferior olive, consistent with a prenatal onset of the disorder. However, studies retrospectively examining head circumference measurements suggest that a major neurological event, overgrowth of the cortex, occurs post-natally. The over-arching implication from the studies by Lainhart et al. [9], Stevenson et al. [10], Courchesne et al. [17] and Cody Hazlett et al. [16] is that brain enlargement in autism is a post-natal phenomenon,

Table 1
Findings from MRI studies of autism on overall brain volume

Study	Subjects	Age range in years	Cognitive ability*	Main finding(s)	Analysis approach
Piven et al. [11]	15 AUT	18–53	PIQ = 92.5	Increased mid-sagittal brain area in autistic group	Adj. for age and IQ
	15 TD		PIQ = 99.9		
	15 TD		PIQ = 130.0		
Piven et al. [12]	35 AUT	14–29	PIQ = 91.0	Increased TBV in autistic group	Adj. for height, IQ, and gender
	36 TD		PIQ = 102.1		
Courchesne et al. [13]	60 AUT	–	PIQ = 36–122	Increased TBV in younger AUT children (2–4)	
	30	2–4		Decreased TBV in older AUT children (5–16)	
	30	5–16		Increased white matter in young AUT children	
	52 TD	–	PIQ = 90–140	Decreased white matter in older AUT children	
	12	2–4		Increased gray matter in young AUT children	
	40	5–16			
Sparks et al. [14]	45 ASD	3.2–4.6	AE = 25.9	Increased TBV in ASD group vs. TD children	Adj. for gender and age
	12 DD	3.1–4.9	AE = 25.5	Increased TBV in ASD group vs. DD children	
	23 TD	3.1–4.7	Average AE		
Aylward et al. [15]	67 AUT	–	FSIQ = 102.7	Increased TBV in young AUT children (<12 years)	Adj. for height
	23	8–12		Increased head circumference in AUT group	
	20	12–18		No TBV differences in older children or adolescent AUT	
	24	18–46			
	83 TD	–	FSIQ = 107.0		
	28	8–12			
	27	12–18			
	28	18–46			
Herbert et al. [34]	17 AUT	7–11	PIQ > 80	n.s. increase in TBV of AUT group ($p = .08$, ES = .67)	
	15 TD	7–11	PIQ > 80	Increased white matter and diencephalon in AUT	Adj. for age and scanner type
Lotspeich et al. [27]	13 LFA	7–17	PIQ = 46	Increased gray matter in LFA and HFA vs. TD	Adj. for age, IQ, and scanner site
	18 HFA		PIQ = 105		
	21 ASD		PIQ = 104		
	21 TD		PIQ = 113		
Palmen et al. [28]	21 AUT	6.9–14.6	FSIQ = 106	Increased TBV and gray matter in AUT	
	21 TD	7.3–14.4	FSIQ = 102	Increased frontal gray, white, parietal gray, temporal gray in AUT	
Cody Hazlett et al. [16]	51 AUT	18–35 months	IQ = 54.1	Increased gray, white and TBV in AUT vs. CON (TD + DD)	Adj. for age and gender
	11 DD		IQ = 58.5	Increased gray, white and TBV in AUT vs. DD	
	14 TD		IQ = 108.1	Increased white matter in AUT vs. TD	

AUT, autism; TD, typically developing; PIQ, performance intelligence quotient; TBV, total brain volume; IQ, intelligence quotient; ASD, autism spectrum disorder; LFA, low-functioning autism; HFA, high-functioning autism; FSIQ, full-scale IQ; DD, developmental delay without autism; CON, controls.

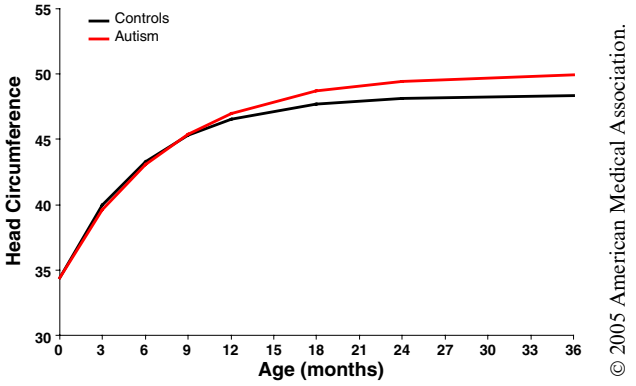

Fig. 1. Growth trajectory of head circumference by group. Depicts increases in cm of head circumference for both autistic and typically developing children over time [16]. Archives of General Psychiatry, 2005, 62, 1366.

occurring in the latter part of the first year of life. While this is not inconsistent with the findings from Bauman and Kemper [18], the different timing for each of these events suggests that they may play unique roles in the development of autistic symptoms.

Evidence from behavioral studies of autism suggests that brain overgrowth may be tied to the onset of the core features of autism. The defining features of autism, as denoted in the DSM-IV, are not observed consistently until 2 years of age or later [19–21]. However, recent studies examining infant siblings of autistic individuals – who are themselves at high risk for symptoms of pervasive developmental disorder – are shedding new light on the early trajectory of autism, and show an interesting convergence with the findings from the recent head circumference and MRI study by Cody Hazlett et al. [16]. Zwaigenbaum et al. [22] observed that, at 12 months of age, infant siblings of children with autism, who were later diagnosed with autism at 24 months, exhibited significant abnormalities compared to infant siblings of children with autism who were not diagnosed with autism at 24 months. Specifically, infants later diagnosed with autism demonstrated impairments in visual disengagement, visual tracking, reactivity, orienting to their name, eye contact, imitation, social smiling, social interest, and sensory-oriented behaviors at 12 months of age. The two groups of children *did not* differ on these behavioral markers at 6 months of age. Although this study did not exclude the possibility that there are more subtle impairments at 6 months that its measures failed to detect, there is no question that there were marked behavioral differences, including the emergence of unequivocal social impairments, between 6 and 12 months [22]. Moreover, Landa and Garret-Mayer [23], using a similar study design, report motor and language delays at 14 months but not at 6 months in infant siblings subsequently diagnosed with pervasive developmental disorders. Together, these findings suggest that behavioral and developmental changes observed between 6 and 12 months may coincide with and even be secondary to brain overgrowth in autism. Although highly speculative, this hypothesis raises the possibility that interventions (as yet unspecified) aimed at preventing brain overgrowth at this early age, could potentially impact the onset of the more classical, defining features of autism. Clearly, large-scale, prospective imaging studies of this very young, high risk age group, together with serial behavioral assessments, will be necessary to more definitively elucidate potential cause and effect relationships.

4. The trajectory of brain growth in autism

The critical importance of longitudinal MRI studies has been convincingly documented by the landmark study of Giedd et al. [24], which showed peak cortical gray matter volume development well into the adolescent years, whereas previous cross-sectional studies had concluded that gray matter volume peaked at 4 years of age. This study demonstrated the necessity of longitudinal research in the presence of substantial inter-individual variation and non-linear growth. The clinical and etiologic heterogeneity in autism is widely recognized [for a review, see [25]. It seems reasonable to assume that, as in the typically developing brain, brain development in autism is likely to proceed over a non-linear course with substantial variability among affected individuals [26]. However, while several longitudinal MRI studies of autism are currently underway, only cross-sectional assessments have been reported to date.

Although Courchesne et al. [17] have hypothesized a complex pattern of decreased brain volume at birth, followed by early overgrowth from ages 2 to 4 years and subsequent slowed growth and declining volume by the late adolescent or adult years, it seems premature to draw such conclusions from the extant data. MRI studies of older children, adolescents and adults have shown some evidence for brain enlargement [11,15,27–29], although the effect may be more robust in early childhood. Aylward et al. [15] reported overall brain enlargement in an 8- to 12-year-old age group, but failed to detect enlargement in individuals between 12 and 46 years. Lotspeich et al. [27] and Palmen et al. [28] each reported enlargement of gray matter volume in samples that included school-aged and adolescent children. Herbert et al. [30] observed selective enlargement of cortical white matter in a small sample of high-functioning autistic (HFA) children (5–11 years), and Piven et al. [11,12] have reported brain enlargement in two independent samples of individuals ranging in age from 12 to 53 years. Together, these studies suggest that enlargement of the brain is detectable in older children, adolescents and adults with autism, though the trajectory of development over time remains to be characterized. Several hypotheses emerge from these results, including (1) enlargement noted at early ages plateaus and continues at a fixed difference over time, (2) an increased rate of growth continues after age 2 years, or (3) after a robust period of overgrowth in early childhood, the brain in autistic individ-

uals decreases in volume relative to controls, as hypothesized by Courchesne et al. [17]. These hypotheses remain to be examined within the context of longitudinal MRI studies.

5. The pattern of cerebral cortical enlargement

Two additional questions regarding patterns of brain overgrowth also have received recent research attention: (1) Is the brain in autism characterized by generalized overgrowth or region-specific enlargement? (2) Are both gray and white matter affected? Piven et al. [29] initially used a semi-automated technique to divide the brain into cortical lobes based on the method of Talairach and Tournoux [31] and subsequently re-examined patterns of enlargement throughout cortical regions in this same sample with a second generation version of the Talairach coordinate approach with updated anatomical landmarks [32]. The updated analyses revealed enlargement in the frontal, temporal, and parietal, but not occipital lobes. Employing a manually defined lobe parcellation method with a sample of 2- to 4-year-old children with autism, Carper et al. [33] reported a similar pattern of enlargement (frontal, temporal, parietal but not occipital). Recently, Cody Hazlett et al. [16] reported generalized brain enlargement in frontal, temporal, and a combined parietal-occipital region in a large sample of 2-year-olds with autism. Enlargement was present in all regions, but varied from an increase of 9% in temporal lobe white matter to 4% in parietal-occipital gray matter. In general, these findings suggest that enlargement is present throughout the brain. Findings by Cody Hazlett et al. [16] in the combined parietal-occipital lobe region may obscure a possibility of increased parietal but not occipital lobe volume in autism at age 2 years. Further research into patterns of overgrowth across cortical lobes is warranted.

Studies have suggested that white matter overgrowth is the primary abnormality in autism. Herbert et al. [34] observed white but not gray matter enlargement in a sample of 32 males between 7 and 11 years, suggesting dissociation between these tissue types. The authors subsequently reported, in a smaller sample of children and adolescents, that white matter enlargement in the cerebral cortex was confined to the 'outer zone' only, which is thought to contain almost entirely intrahemispheric corticocortical fibers [30]. The findings from this study lead to the hypothesis that autism is characterized by abnormalities of connecting fibers, specifically those between distant regions of the brain. Consistent with this hypothesis, functional MRI studies also have suggested that decreased cortical connectivity underlies complex verbal and nonverbal processing impairments in autistic adults [1,2]. These results, along with consistent reports of decreased corpus callosum volumes (reviewed below) and a report of smaller, but less compact minicolumns on post-mortem analysis of the cerebral cortex [35], suggest that autism may be characterized by morphometric abnormalities and resultant impaired functioning of the integrative circuits that typically mediate communication between cortical regions.

Despite reports suggesting that overgrowth is confined to white matter in autism, several studies have observed enlargement of both cortical and subcortical gray matter. Carper et al. [33] reported white matter enlargement in frontal and parietal lobes and gray matter enlargement in frontal and temporal regions. Lotspeich et al. [27] studied 52 children 7.8–17.9 years of age and found evidence of cortical gray matter enlargement. Cody Hazlett et al. [32] reported a pattern of left-sided gray matter volume increase in an adolescent and adult sample with autism and Cody Hazlett et al. [16] observed both gray and white matter volume to be increased in a large sample of 2-year-olds with autism. More fine-grained analysis of this latter sample suggested that while white and gray matter volume differences were present in comparison to developmentally delayed (non-autistic) controls, only white matter volume differences were detected in comparison to typically-developing controls. These results highlight the importance of interpreting findings in autism, a disorder known to be highly heterogeneous and associated with mental retardation, relative to IQ-comparable controls. The absence of findings related to gray matter volume in some studies may be the result of those studies either being limited to normal IQ autistic individuals (as in [30 and 34]) or due to employment of typically-developing controls only (in comparison to autistic subjects with and without mental retardation). In addition, variation across studies may be the result of age effects as the studies by Cody Hazlett and co-workers suggested only gray matter effects in adolescents and adults; whereas both gray and white matter volume increase was observable in 2-year-olds with autism.

6. Clues to the pathogenesis of autism

Clarification of the neuroanatomical phenotype as it develops over time in autism may inform neurobiological studies aiming to understand the pathogenesis of this disorder. Clearly, the postnatal onset of brain enlargement suggests that factors underlying dendritic arborization and synaptogenesis (e.g., dendritic pruning) may have more critical roles in brain overgrowth in autism than much earlier appearing phenomena such as neurogenesis [36]. More refined examination of the temporal pattern across cortical regions and tissues may also contribute important information towards understanding the underlying neurobiology. As an example, Monuki and Walsh [37] identified two transcriptional regulators, Emx2 and Pax6, that are expressed in the cortical ventricular zone and regulate the relative size of cortical areas. Emx2 and Pax6 are expressed in graded and opposing fashion in the cortex, going from high posterior to low anterior. Loss of Emx2 results in mice with marked size reductions of posterior cortical areas (including hippocampus). These mice also show shifted or expanded anterior neocortical regions (including motor areas). Correspondingly, loss of Pax6 function results in decreased

anterior neocortical size. In humans heterozygous for Pax6 mutations, subtle alterations in forebrain size and shape are observed.

Molecules that regulate axon guidance, such as those that mediate cell–cell interactions, are among the most likely transcriptional targets of such genes. As such, the ephrin/Eph receptor system, in particular, seems to have a general role in the formation of topographic maps in the brain. Another gene of interest, Microcephalin (*MCPH1*), has been shown to regulate brain size in animal models and has a non-synonymous single nucleotide polymorphism (SNP) (rs930557) that has been associated with variation in brain size in humans [38]. ASPM (abnormal spindle-like associated microcephaly) is a related gene with similar phenotypic effects that contains two polymorphisms (rs3762271 and rs964201) that may be related to individual brain size [39]. Mutations in human genes that regulate later events in cortical patterning may not cause gross malformations of the cortex but instead produce more subtle cognitive, behavioral and language deficits such as the speech and language deficits caused by mutation of the FOXP2 transcription factor gene in autism [40]. Similarly, other candidate genes known to play a role in neurogenesis, such as the serotonin receptor transporter [41,42], may have a specific impact on patterns of cortical development in autism. Intermediate brain phenotypes (e.g., cortical volume enlargement or a specific pattern of enlargement across tissues and regions) may prove to be of critical importance in finding autism genes through linkage and association studies, although longitudinal growth estimates may be more informative than cross-sectional measures.

7. Subcortical and posterior fossa structures in autism

The study of the volume and shape of selected subcortical structures in autism traditionally has been of interest given what is understood about the modularity of the brain and the hope that specific brain-behavior relationships can be identified in autism.

7.1. Basal ganglia

Volume differences have been reported in the caudate nucleus (CN) in studies of obsessive-compulsive disorder (OCD), Fragile X Syndrome and Tourette's Syndrome, disorders with phenomenological overlap with the repetitive behaviors and restricted interests characteristic of autism [43–46]. Sears et al. [47] first suggested that the CN was increased in volume in two independent samples of adolescents and adults with autism. These investigators also reported that CN enlargement was associated with the severity of repetitive behaviors as measured by the Autism Diagnostic Inventory (ADI). Significant positive correlations were observed between motor stereotypies and CN volume in an adolescent and adult sample of autistic individuals and significant negative correlations were observed between CN volume and two additional items – degree of upset with change in environment and routine and severity of compulsions and rituals. These findings suggest that different fronto-striatal pathways (e.g., dorsal and ventral) may be involved in these related phenomena [48,49]. More recently, Cody Hazlett et al. [50] found enlargement of the CN (beyond the enlargement explained by an overall increase in brain volume) in their 2-year-old sample of autistic children. A pattern of clinical correlates identical to those reported by Sears et al. [47], with a significant positive correlation with lower order motor stereotypies and a significant negative correlation with higher order repetitive behaviors such as distress over change in the environment or routine, also was observed. Hollander et al. [51] reported basal ganglia enlargement in a sample of adults with autism spectrum disorders, but suggested that, unlike the findings reported by Sears et al. [47] and Cody Hazlett et al. [50], enlargement was *positively* associated with higher-order repetitive behaviors (e.g., insistence on routine).

7.2. Amygdala

A wealth of animal, functional MRI, and human lesion studies have implicated the amygdala in emotion, social judgments, social attention, social cognition [for a review, see [52]], and autism [53]. While this hypothesis may not encapsulate the multiple interconnected neural systems underlying autistic pathology, the relevance of the amygdala to understanding the neural circuitry of autism is well established. Several structural MRI investigations in moderate-sized samples have shown enlarged amygdala volumes in individuals with autism relative to age-matched controls [14,54–57]. Schumann et al. [57] suggested that amygdala enlargement in autism is an age-dependent phenomenon, observing amygdala enlargement in school-aged children (7.5–12.5 years) but not in adolescents (12.5–17.5 years) with autism. Consistent with this, Mosconi et al. [55] and Sparks et al. [14] observed that the amygdala was enlarged in samples of 18–35-month and 3- to 4-year-old children, respectively. Analyses of the neuropsychological correlates of amygdala enlargement have been limited thus far. Sparks et al. [14] first reported enlargement of the amygdala in children with DSM-IV autistic disorder compared to more mildly affected children with pervasive developmental disorder – not otherwise specified (PDD-NOS). Others have suggested that amygdala enlargement may be associated with severity of social-communicative abnormalities [58], though research into the timing and specific nature of this relationship (i.e., which social skills are related to amygdala function) is needed.

7.3. Corpus callosum

The corpus callosum (CC) is the major axonal pathway bridging the two cerebral cortical hemispheres. The integrity of the CC often is used as an index of general connectivity. In reality, the proportion of cortical fibers that cross at the CC actually is quite small (approximately 2–3%) and

inferences regarding connectivity extrapolated from findings of morphological differences in the CC are questionable [59,60]. MRI studies of the CC in autism have been consistent in showing a decrease in size of the CC (generally a decrease relative to the overall volume of the cortex), although attempts to localize the effect to specific subregions have yielded inconsistent results [61–64]. The finding of decreased size of the CC in autism is consistent with the hypotheses by Herbert et al. [30] that axonal projections within the basal forebrain are decreased, and Casanova [65], who reported minicolumnar abnormalities in autism. Both of these investigators hypothesize that associational fibers may be reduced in the brain in autism resulting in a functional disconnectivity.

Findings of reduced CC size may offer an index of overall disconnectivity in autism and provide clues to the cortical layers implicated in increased brain size as only selected layers (e.g., cortical layer III) contribute axons that cross at the CC [66,67]. Recently, Cascio et al. [68] utilized tractography to define subregions of the CC on the basis of their projections to specific cortical lobes. The authors reported no evidence of a correlation between the size of these CC subregions and specific cortical lobe white matter volumes in a group of children with developmental delay, but significant, robust correlations were observed between CC subsections and corresponding cortical lobe white matter volumes in typically developing children. These findings suggest that the CC may be an indirect measure of connectivity in the brain. Further study of the development of the CC and its projections over time in the developing brain in autistic individuals clearly is warranted.

7.4. Cerebellum

Post-mortem studies consistently have shown a decrease in Purkinje cells in the cerebellum in autism [69,70]. MRI studies of the cerebellum have been less consistent. Early reports of selective hypoplasia of the neocerebellar vermis (lobules VI–VII) [71] have not been replicated by independent laboratories [11,14,28,64,72–74], except in instances when confounding factors (e.g., comparability of IQ or gender in cases and controls) have not been sufficiently taken into account [75,76].

Studies examining overall cerebellar volume have been somewhat inconclusive. Courchesne et al. [13] noted that both cerebellar gray and white matter were increased in volume in a small sample of 2- to 4-year-olds with autism. Similarly, Sparks et al. [14] suggested that total cerebellar volume was enlarged in proportion to increases in total brain volume among 3- to 4-year-olds with autism. Piven et al. [64] employed a semi-automated technique based on Talairach and Tournoux [31] coordinates and reported an overall increase in cerebellar volume among adolescents and adults with autism. In contrast, employing an automated deformation-warping method based on an atlas of the 2 year old brain, Cody Hazlett et al. [16] reported that cerebellar gray and white matter volumes were not enlarged in 18- to 35-month-old children with autism compared to either age-matched typically developing children or age and IQ-matched developmentally delayed children without autism.

Currently, findings regarding the cerebellum are difficult to interpret but suggest that if enlargement is present, it may have its onset after age 2 years. Future longitudinal research is needed to investigate whether neuroanatomic abnormalities localized to the cerebellum are later-occurring phenomena.

8. Future directions and conclusions

This is an exciting time for MRI studies of autism. While the hope for specific structure – function relationships has not been as forthcoming as anticipated, the striking overgrowth of the brain that appears to have its onset in the latter part of the first year of life, perhaps in concert with the behavioral onset of the disorder, presents many new directions that must now be explored. The paradigm of longitudinal 'baby sibling' studies of the very young developing brain is a particularly promising direction that will need to be explored with MRI. Structural MRI is suitable for studying young children over the course of development. This method does not have the limitations of functional MRI, which typically requires active participation by the subject, or positron emission tomography (PET), which emits ionizing radiation that limits the frequency with which individuals may be safely scanned. Structural MRI is ideally suited for the serial scanning in longitudinal studies that is necessary for describing early brain development in a complex disorder such as autism. New approaches to scanning infants and toddlers involving development of hardware for rapid scanning (e.g., parallel head coils) and automated image processing approaches for efficiently and reliably differentiating early gray and white matter development in large samples are now available [77]. Methods for acquiring scans from young children that involve behavioral training and desensitization in a "mock", or practice scanner environment, also are now widely available in many centers to facilitate imaging these children without sedation. In addition, studies of the use of conscious sedation for neuroimaging young children have now shown that it is safe and practical in children with autism and developmental delay [78].

Studies of the pattern of brain enlargement in autism suggest that a diffuse and complex set of processes is likely to be involved, affecting gray and white matter, as well as cortical and subcortical regions. Enlargement has been detected in both gray and white tissue throughout the cortical lobes. The finding of increased white matter suggests that more detailed description of white matter properties and tracts, using diffusion tensor imaging (DTI), will be important for understanding neuropathological mechanisms underlying autism. The recent development of DTI holds great promise for mapping white matter fiber tracts within the developing brain and exploring their relationship

to changing clinical features. To date, inferences about functional subdivisions of the brain have been based largely on definitions of structural borders (e.g., sulci and gyri) that may have limited correspondence to functional subunits of the brain. DTI can be used to characterize properties of white matter (including architecture, amount, and directionality of water diffusion), with implications for structural connectivity between regions and structures of the brain.

MRI studies of autism have been plagued by small sample sizes and inconsistencies in design that have resulted in limited power to deal with the heterogeneity of this condition. Large-scale, longitudinal studies will partly address this issue. In addition, studies have varied in their methods to control for IQ differences between autistic and non-autistic groups. Approximately 75% of affected individuals have IQs in the mentally retarded range, suggesting that IQ is an important index of heterogeneity that must be taken into account.

Due to the low prevalence of females with autism, particularly in the higher IQ groups, gender differences in autism also have not been adequately assessed. Among the six recent studies that have investigated gray and white matter volumes in autism, only one included females, and only six of the 219 autistic subjects included in these studies were female. Sexual dimorphism in the development of cortical and subcortical structures in the brain is well documented in typically-developing individuals [24,26,79,80], suggesting that understanding gender differences in brain morphology in autism may be particularly important. Caviness et al. [80] have further suggested that school-age males and females have significantly different volumes of selected gray matter structures, especially the caudate nucleus and amygdala – two substructures that have been implicated in MRI studies of autism.

In summary, research using high-resolution MRI over the past decade has stimulated exciting new hypotheses about the brain mechanisms that may underlie the development of autism. Findings of brain overgrowth having its onset in the latter part of the first year of life, concurrent with the onset of the defining symptoms of autism, present a new perspective on the timing and pathogenesis of this condition. The temporal overlap of these biological and behavioral features suggests that brain enlargement may contribute to the onset of symptoms and be a target for future treatments. Lesion-function hypotheses may fail to capture the complexity of pervasive brain and behavior dysfunction underlying this developmental disorder. Structural MRI studies following brain changes and their associated behavioral developments in children with autism over time will undoubtedly provide new insights into the pathogenesis of this disorder.

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