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Brain imaging research in autism spectrum disorders: in search of neuropathology and health across the lifespan

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Abstract

Purpose of review—Advances in brain imaging research in autism spectrum disorders (ASD) are rapidly occurring, and the amount of neuroimaging research has dramatically increased over the past 5 years. In this review, advances during the past 12 months and longitudinal studies are highlighted.

Recent findings—Cross-sectional neuroimaging research provides evidence that the neural underpinnings of the behavioral signs of ASD involve not only dysfunctional integration of information across distributed brain networks but also basic dysfunction in primary cortices.

Longitudinal studies of ASD show abnormally enlarged brain volumes and increased rates of brain growth during early childhood in only a small minority of ASD children. There is evidence of disordered development of white matter microstructure and amygdala growth, and at 2 years of age, network inefficiencies in posterior cerebral regions.

From older childhood into adulthood, atypical age-variant and age-invariant changes in the trajectories of total and regional brain volumes and cortical thickness are apparent at the group level.

Summary—There is evidence of abnormalities in posterior lobes and posterior brain networks during the first 2 years of life in ASD and, even in older children and adults, dysfunction in primary cortical areas.

Keywords

autism spectrum disorder; brain; imaging; longitudinal; MRI

INTRODUCTION

Qualitative abnormalities of social interaction and social communication cluster with stereotyped repetitive interests and behaviors within individuals, become observable during

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Conflicts of interest

None.

the first year of life, and usually cause lifelong impairment, for reasons we still do not understand. Neuroimaging has the potential to help elucidate what has gone wrong, what continues to go wrong, what has gone right, and what can be improved [1–3] in brain development in autism spectrum disorders (ASD). This review highlights a selection of recent advances from more than 200 original research publications in the past 12 months.

CROSS-SECTIONAL IMAGING STUDIES OF IDIOPATHIC AUTISM SPECTRUM DISORDERS

The intense, restricted, repetitive, and often driven interests that impair many individuals with ASD appear to have similar and different neural underpinnings compared to the strongly preferred hobbies and interests of typical developing individuals. The similarity is activation of bilateral amygdala, and the difference is significantly increased activation of the left anterior insula and anterior cingulate gyrus in ASD in response to pictures of one's own interest [4▪]. The anterior insula and anterior cingulate gyrus are key nodes of the salience neural network, which appears spatially restricted at the structural level [5] and overconnected within itself at the functional level in ASD [6]. Dysfunction of the salience neural network seems to be involved in socio-emotional impairment as well as restricted repetitive behaviors and interests [6,7].

Children with ASD who have exaggerated negative responses to sensory stimuli have heightened functional activation in sensory processing areas, including primary sensory cortices, and in emotional processing and regulating areas of the brain including the amygdala and prefrontal cortex [8]. These brain regions are significantly over-reactive to sensory stimuli, even after individual differences in anxiety are controlled for. Different age-related changes in gray and white matter volumes in the Heschl's gyrus are present [9]. Atypical sensory processing may be related to focal cortical dysplasias in ASD [10] and to atypical microstructure in the inferior longitudinal fasciculus and splenium of the corpus callosum [11].

Cognitive and behavioral inflexibility such as insistence on sameness and other rigid patterns of thought and behavior, may reflect dysfunction of basic neural mechanisms. When a stimulus is presented multiple times, brain activation, as measured by functional brain imaging, normally shows repetition suppression, that is, a decrease in activation in category-selective cortical areas. A tendency toward decreased repetition suppression has been reported in children with ASD and their first-degree relatives. In neurotypical adults, individual variation in the level of autistic traits is associated with individual differences in repetition suppression; as autistic traits increase, habituation and adaptation in the brain to repeated stimuli decrease [12▪]. Parents of ASD children may also have increased activation of the amygdala and fusiform gyrus in response to faces [13].

When children with ASD perform a set-shifting task, magnetoelectroencephalography results suggest abnormal temporal organization and dynamics in distributed large-scale neural assemblies, preventing the global brain interactions needed for efficient performance of the task [14]. Precise temporal orchestration of network functioning, essential for accurate higher-order sensory processing and appropriate behavioral response [15], may be disrupted

in ASD by cortical dysfunction and abnormalities of structural connectivity, including myelination [16–18]. Maturation of cognitive control performance and brain circuitry appears atypical in ASD during adolescence [19]. Functional connectivity appears to increase between brain regions supporting reactive 'last-minute' cognitive control (i.e. anterior cingulate cortex and ventrolateral prefrontal cortex) in young people with ASD, rather than between brain regions supporting proactive cognitive control (i.e. dorsolateral prefrontal and parietal cortices) [20]. Modulation and normal differentiation of brain states may also be impaired [21].

Abnormal integration of information in distributed brain networks may underlie many core clinical features of ASD, but there is additional evidence of basic neural dysfunction in primary sensory and motor cortical areas and in the thalamus, well before the stage of higher-order integration [22,23]. Basic deficits in visual motion processing in individuals with ASD seem to be related to specific dysfunction in primary visual areas where motion is first detected [24▪].

Different microstructural changes may differentiate language impairment in ASD from other language disorders. Non-ASD children with specific language impairment have atypically increased radial diffusivity in the arcuate fasciculus, indicating an alteration in microscopic architecture that results in a net increase in water diffusion perpendicular to the white matter tract fibers. ASD children with language impairment have increased mean axial diffusivity, pointing to white matter microstructural changes that result in a net increase in water diffusion parallel to arcuate fasciculus fibers [25]. Impaired language processing in ASD is also associated with decreased functional synchronization within the language neural network, atypical distribution of the work involved in processing language, differences in how specific language regions of the brain are recruited, but also some positive changes in age-related maturation of the network [26].

LONGITUDINAL IMAGING STUDIES OF IDIOPATHIC AUTISM SPECTRUM DISORDERS

Despite many claims in the literature about how the brain is changing over time in ASD from infancy to adulthood, there has been little longitudinal evidence to support the claims [27▪▪]. Table 1 [27▪▪,28–38,39▪] summarizes longitudinal neuroimaging studies of individuals with ASD published to date.

Infancy and early childhood

Longitudinal neuroimaging studies of ASD during very early childhood are conducted in two different types of samples: infants at high risk of developing ASD (because they have an older sibling with ASD) recruited before it is known whether or not the infants will develop ASD, and very young children with ASD recruited shortly after they are diagnosed.

The mean brain volume of high-risk infants who develop ASD is normal at 6–9 months of age, but it is increased by 12–15 months of age [38,40]. Mean rate of brain growth is faster between 6 and 24 months. The mean volume of extra-axial fluid (in the subarachnoid space) is increased by 6 months of age, particularly over the front of the brain, and it is still

increased at 18–24 months of age. More fluid at 6 months of age predicts more severe core features of ASD at 24 months of age. Extra-axial fluid and increasing cerebral volume independently contribute to the abnormally increased head circumference observed during the first 2 years of life in some infants who develop ASD [38]. But in a very large prospective study of head circumference in high-risk infants during the first 3 years of life, rate of head growth did not predict which infants developed ASD [41].

In young children scanned after they are diagnosed with ASD, mean cerebral volume and total gray and white matter volumes are increased [31,37], with the most robust effect in the temporal lobe. The growth rate of cerebral volume between 1.5 years and 4.5 years of age was atypically increased in one study, but was normal in another study. A recent cross-sectional study of young children with ASD found no increase in mean total brain, total tissue, or total white matter or gray matter volumes [42]. These results, along with the mixed findings of longitudinal studies of head circumference during infancy and early childhood, question whether ‘early brain overgrowth’ in ASD truly exists [43]. True brain overgrowth, that is, an abnormally enlarged brain, and abnormally rapid rate of brain growth during the first years of life seem to occur in a very small subgroup of ASD children, sometimes in association with general body overgrowth [44]. Increased head size is a weak indicator of affected status in simplex families [45].

Mean amygdala volume is increased bilaterally in young children with ASD between 2 and 4 years of age and 1–2 years later [35,36]. The increase in the right amygdala is out of proportion to total cerebral volume. By 6–7 years of age, volumes of right and left amygdalae appear increased, predominantly due to expansion of the laterobasal subregion [46]. Rate of amygdala growth appears atypically increased in some young children with autism [35,36]. Larger amygdala size is associated with more severe core features of ASD and worse 2-year developmental course and outcome in some studies [46–48], but with better joint attention in one study [35].

Mean fractional anisotropy, a measure of white matter integrity, is increased at 6 months of age in high-risk infants, but by 24 months of age it has normalized in some tracts and decreased in other tracts [49]. The longitudinal trajectory of fractional anisotropy between 6 and 24 months of age is atypical in 80% of the white matter tracts examined in high-risk infants, suggesting widespread involvement. At the whole-brain neural network level, network inefficiency appears decreased at 24 months of age in high-risk infants who develop ASD [50▪▪]. The topography of the structural networks appears reduced in spatial extent and number of connections. Connections that do exist are weaker than in infants who do not develop ASD. The differences in network efficiency are located primarily in posterior (occipital and temporal) regions of the brain involved in processing auditory, visual, language, and nonverbal social stimuli, rather than in frontal regions. Greater network inefficiency is associated with greater severity of core features of autism [50▪▪].

Longitudinal studies of brain chemicals in children with ASD show stable, normal concentrations of brain lactate at 3–4, 6–7, and 9–10 years of age [51]. Mean concentrations of N-acetylaspartate, choline, creatine, and glutamine + glutamate are decreased in children with ASD at 3–4 years of age, but normal by age 9–10 years [52].

Later childhood, adolescence, and adulthood

Mean total cerebral volume appears modestly increased in early childhood but then it decreases in idiopathic ASD in contrast to typical development. The ASD and typically developing growth curves cross during early adolescence. The ASD curve then declines more than the typical curve into young adulthood [27▪▪]. Decreasing total cerebral volume in ASD from late childhood into adulthood appears mainly due to a reduced rate of lobar white matter volume growth [27▪▪]. The growth curve of total corpus callosum volume is similar in idiopathic ASD and typical development, although there may be some localized volumetric decreases [27▪▪,29]. At the subregional level, preliminary tensor-based morphometry results show a reduced rate of white matter growth in late childhood and early adolescence in posterior lobes, particularly left parietal, bilateral temporal, and left occipital regions [32].

Tensor-based morphometry results do not detect significant ASD–control differences in age-related change in gray matter between late childhood and adolescence [32]. When larger samples are examined using traditional volumetric and cortical thickness approaches, decreased growth of right Heschl's gyrus gray matter [9], decreased occipital lobe cortical thickness [30], and increased volumetric growth of the caudate nucleus [34] and the brainstem [39▪] are reported. When regional cortical gray matter volumes are comprehensively examined from late childhood through young adulthood, more striking differences in ASD are found [27▪▪,39▪]. At the lobar level, posterior rather than frontal lobes gray matter appears most affected, with the most robust effect in the occipital lobe followed by the parietal lobe. Overall, mean cortical thickness is somewhat increased during childhood in ASD, has a steeper decline during adolescence with the ASD curve crossing the typical development curve leading to decreased mean cortical thickness in adulthood [39▪]. When intelligence quotient (IQ) is controlled, the evidence suggests a posterior-to-anterior developmental gradient: thicker occipital lobe cortex during childhood is followed by excessive thinning in some frontal lobe regions during adolescence, and by cortical thinning in some parietal areas and widespread cortical thinning in the frontal lobes in adulthood [39▪].

Mean amygdala volume and rate of growth appear normal in older children with ASD followed for 2 years [28]. A recent large cross-sectional study of ASD individuals 6–65 years of age also found no significant ASD–control difference in mean amygdala volume [53]. Age-related changes in size of the amygdala from young to mid-adulthood in ASD can only be inferred from a large cross-sectional study: amygdala volume seems to increase in typical adults but not in adults with ASD [54].

The clinical meaning of altered developmental trajectories of brain volume during late brain development and maturation in ASD is not known. Results of studies examining longitudinal growth trajectories of white matter microstructure during this period in ASD are pending [55]. Elevated levels of brain lactate may develop in localized areas of the brain in some ASD adults [56]. Brain lactate is elevated in mitochondrial disorders, some cases of bipolar disorder, and transiently by subtle hyperventilation and caffeine [50▪▪].

AUTISM SPECTRUM DISORDERS ASSOCIATED WITH SPECIFIC GENETIC DISORDERS

Young children with fragile X syndrome (FXS) have much larger caudate volumes, smaller amygdala volumes, and similar global brain volumes compared to children with idiopathic ASD, and rates of brain growth are similar and normal between 2–3 and 4–5 years of age. Brain–behavior correlations are different; caudate volume robustly correlates with compulsive and ritualistic behavior in young children with idiopathic ASD, but with self-injurious behavior in young children with FXS [57]. Tuberous sclerosis complex (TSC) with ASD is characterized by smaller corpus callosum volume and greater abnormalities of white matter microstructural integrity in the corpus callosum and arcuate fasciculus compared to TSC without ASD [58]. At the level of whole brain functional neural networks, TSC is characterized by global underconnectivity and altered network topology, regardless of whether or not autism is present [59▪]. In contrast, ASD, regardless of whether it is idiopathic or associated with TSC, is characterized by decreased long-range connectivity, a proportional increase in short-range connectivity, and evidence of decreased functional specialization and excessive degeneracy within the network [57]. Neuroimaging studies of individuals with different types of 16p11.2 copy number variations with and without autism are underway [60,61].

HETEROGENEITY, VARIABILITY, AND MULTIPLE PERSPECTIVES

There is substantial individual variation in all brain measures [12▪]. Small control samples used in the majority of neuroimaging studies of ASD may not adequately represent the distribution of normal variation against which ASD measures are compared [62▪]. Large variability in how a construct, such as theory of mind, is defined and operationalized and how its brain correlates are measured are also problematic [63]. Different types of imaging, image analysis methods, and clinical measures applied within the same individuals may be essential to best understand what is going on in ASD [64,65]. Tremendous biological complexity lies below what appear to be simple measures of brain structure and function [66–68]. Increased consideration of the clinical heterogeneity of ASD has led to characterizing individuals in imaging studies along quantitative dimensions of specific behaviors in addition to diagnosis and diagnostic algorithm scores [8,9,14]. The creation of large publically available ASD neuroimaging databases such as the Autism Brain Imaging Exchange (ABIDE) and the National Database for Autism Research (NDAR), support efforts to replicate results in independent samples [7,69▪,70].

CONCLUSION

In-vivo neuroimaging in ASD has the potential to discover reliable and replicable clinicopathological associations across the lifespan. Such discoveries will help the field move from understanding ASD as clinical syndrome to understanding ASD as the common expression of a variety of different neurodevelopmental diseases with at least somewhat different pathological mechanisms.

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KEY POINTS

- True brain overgrowth, that is, an abnormally enlarged brain, and an abnormally rapid rate of brain growth during the first years of life occur in only a small minority of children who develop ASD.
- Longitudinal neuroimaging studies of the brain in ASD show dynamic changes from infancy through young adulthood.
- Abnormalities in primary sensory cortices appear to be involved in ASD, in addition to neural network dysconnectivity and dysfunction.

Table 1

Longitudinal neuroimaging studies of idiopathic autism

Reference	Samples, mean age at time 1	Age range across all time points	Number of scans analyzed/ participant	Average interscan interval	Imaging	Longitudinal analysis
Barnea-Goraly *et al.*, 2014 [28]	23 ASD, 23 TDC, age: 10.6 yrs., 100% male	8–14 yrs.	2 (73%)	2.0 yrs.	Volumetric, amygdala and hippocampus	Mixed-effects regression
Frazier *et al.*, 2012 [29]	23 ASD, 23 TDC, age: 10.5 yrs., 100% male	8–16 yrs.	2 (80%)	2.3 yrs.	Volumetric, corpus callosum	Mixed-effects regression
Hardan *et al.*, 2009 [30]	18 ASD, 16 TDC, age: 10.9 yrs., 100% male	8–15 yrs.	2 (82%)	2.1 yrs.	Volumetric, lobar cortical thickness	Volumetric change over time; MANCOVA
Hazlett *et al.*, 2011 [31]	59 ASD, 38 TDC, age: 2.7 yrs., 81% male	2–5 yrs.	2 (59%)	2.0 yrs.	Volumetric, total brain, cerebrospinal fluid, and so on	Linear-mixed models with repeated measures
Hua *et al.*, 2013 [32]	13 ASD, 7 TDC, age: 10.5 yrs., 100% male	7–16 yrs.	2	2.9 yrs.	Tensor-based morphometry, whole brain	Annual tissue growth rate maps, permutation tests
Jou *et al.*, 2013 [33]	23 ASD, 23 TDC, age: 10.6 yrs., 100% male	8–17 yrs.	2 (41%)	2.0 yrs.	Volumetric, brainstem	Mixed-effects regression
Lange *et al.*, 2014 [27▪▪]	100 ASD, 56 TDC, age: 17.0 yrs., 100% male	3–35 yrs.	3 (47%) ≥ 2 (76%)	2.6 yrs.	Volumetric, global, regional	Longitudinal mixed-effects, ANCOVA
Langen *et al.*, 2014 [34]	49 ASD, 37 TDC, age: 17.0 yrs., 100% male	7–17 years	2	2.3 yrs.	Volumetric; global brain, striatum	Volumetric growth per years; MANCOVA
Mosconi *et al.*, 2009 [35]	52 ASD, 33 TDC, age: 2.64 yrs., 81% male	18–59 mos.	2	2.0 yrs.	Volumetric, amygdala, total tissue	Mixed model repeated measures
Nordahl *et al.*, 2012 [36]	45 ASD, 25 TDC, age: 37 mos., 100% male	2–4 yrs.	2 (53%)	13 mos.	Volumetric, amygdala, total cranial volume	Volume change over time, ANCOVA
Schumann *et al.*, 2010 [37]	41 ASD, 44 TDC, age: 12–67 mos., 75% male	12–59 mos.	2 (67%) ≥ 3 (33%)	0–25 mos.	Volumetric, cerebral gray, white matter, lobar	Volume change over time, ANCOVA
Shen *et al.*, 2013 [38]	55 total, age: 6–9 mos., 67% male	6–33 mos.	3 (76%)	6.5 mos.	Volumetric, total cerebral, extra-axial fluid, lateral ventricle	Linear mixed model for repeated measures
Zielinski *et al.*, 2014 [39▪]	97 ASD, 60 TDC, age: 16.8 yrs., 100% male	3–43 yrs.	3 (48%) ≥ 2 (76%)	2.8 years	Cortical thickness	Longitudinal mixed-effects, ANCOVA

ANCOVA, analysis of co-variance; ASD, autism spectrum disorder; MANCOVA, multivariate analysis of co-variance; mos., months; TDC, typically developing controls; yrs., years.