Neurological Structure Variations in Individuals with Autism Spectrum Disorder: a Review

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ABSTRACT:
Neurological structure variations in individuals with autism spectrum disorder: a review

Autism spectrum disorder is a neurodevelopmental disorder that is characterized by impairments in social communication and social interactions along with repetitive, stereotypic behaviors and interests. The spectrum is quite broad, and the pathophysiology appears to be related to a number of factors. A common theme is that the disorder is one of impaired brain development. Neuroimaging studies offer a way to investigate impaired brain development by considering structural differences between those with autism and those without. Areas of focus include neuroanatomical regions that correlate with the clinically recognizable features of autism. In this review of structural studies, volumetric variation in terms of grey and white matter and total brain volume and in terms of neurological structures (e.g. frontal lobe, parietal cortex, amygdala, etc.) is discussed. Although a few trends have been noted, much of the literature demonstrates heterogeneity in the reported findings, which likely reflects the heterogeneity of the clinical presentation of this disorder. Further studies will need to correlate these structural findings with functional data and look to better understand the underlying molecular and genetic processes.

Keywords: autism spectrum disorder, neuroimaging, brain, MRI, CT, review

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that often presents in early childhood. Broadly, it is inclusive of autism and Asperger’s syndrome and can overlap with other pervasive developmental disorders. The global prevalence has been estimated at about 62 in 10,000¹, and as of 2014, the Center for Disease Control and Prevention suggests that the prevalence of ASD is about 1.5% (or 1 in 68) in the United States. It occurs about four times more often in males than in females. The rates of diagnosis have gone up, and there are questions as to whether or not the rates have increased due to actual prevalence increases, or secondary to other factors such as the expansion of criteria, differences in study methods, or improved recognition of ASD.

The pathophysiology appears to be connected to a number of factors, which are still generally poorly understood. ASD appears to result from developmental factors that seem to affect the progression of brain development. It has been suggested that changes begin soon after conception and continue to have an impact as individuals age. The characterization of these changes has been the subject of some study. This paper is a short review of the literature examining the structural changes in the brains of those with ASD.

Autism

The Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) lists ASD within
neurodevelopmental disorders². Criteria include persistent deficits in social communication and social interactions across multiple contexts, as well as restricted, repetitive patterns of behavior, interests or activities. Depending on severity, features may be evident as early as the developmental period.

Impairments in communication and social interactions are generally pervasive and sustained. Language deficits can include lack of speech, poor comprehension of speech, echoed speech, and impaired reciprocal social communication. Autistic individuals also demonstrate problems with social reciprocity. They do not initiate social contact, share emotions and, as infants or toddlers, do not engage in imitation of behavior. As adults, individuals may have trouble processing social cues such as knowing when to join a conversation, and what to say and not to say. Eye contact may be inappropriate along with gestures, body postures, facial expressions and voice intonation. There can be difficulty in understanding which behaviors are appropriate in which social situations, and as a result, there may be a preference for solitary activities, or working with others who are much older or much younger. Often coping strategies may be developed, especially into adulthood, but the constant effort can result in a significant amount of anxiety.

A similar range of manifestations is also present for restricted, repetitive patterns of behavior, interests, or activities. Simple motor stereotypies include hand flapping and finger flicking. They may also engage in repetitive use of objects such as spinning coins, or lining up objects. Resistance to change and rigidity towards following the “rules” may be demonstrated. Highly fixated interests can manifest as obsessive-compulsive behaviors. There can also be elements of increased or decreased sensory input issues.

Other features that may be present include intellectual disability (including specific learning disorders), ADHD, epilepsy, anxiety disorders, and mood disorders. The DSM-5 indicates that “about 70% of individuals with autism spectrum disorder may have one comorbid mental disorder, and about 40% may have two or more comorbid mental disorders³”. Females appear to demonstrate intellectual disability more than males, which may indicate that females who do not present with intellectual difficulties may be overlooked from a diagnostic perspective. Hyperactivity, aggression, and self-harming behaviors may also be present³.

The number of symptoms described above reflects the heterogeneity of the presentation of ASD, and this in turn is a reflection of the heterogeneity of proposed etiologies for the development of autism. Given the range of symptoms, it is possible to correlate some of them to specific regions in the brain.

Implicated Regions

Various regions of the brain have been implicated functionally as relating to the various features of autism. Identifying specific regions is challenging given the heterogeneity of presentation; however, using the results of animal studies, lesions studies, post-mortem evaluation, and drawing parallels from other presentations (obsessive-compulsive disorder - OCD, pervasive developmental disorder - PDD, epilepsy, etc.)³, in which structural and functional magnetic resonance imaging (MRI) have been used, one can surmise which areas of the brain would be reasonable to investigate.

Social behaviors appear to correlate with function in the frontal lobe (orbitofrontal cortex, inferior frontal gyrus, anterior cingulate gyrus), superior temporal cortex (and sulcus), the fusiform gyrus, parietal cortex and the amygdala. Expressive language function has primarily been associated with Broca’s area in the interior frontal gyrus, along with portions of the supplementary motor cortex. Receptive language is often associated with Wernicke’s area. Association circuits connect the two areas and can be impacted as well, affecting language processing and social attention. Language is usually associated with the dominant hemisphere. Regions of the cerebellum also appear to have a role in communication, helping modulate emotion, language and executive function⁴. From
studies involving patients with OCD, it appears that the orbitofrontal cortex, the anterior cingulate cortex, thalamus, and the caudate nucleus have a role in the expression of repetitive and stereotyped behaviors. Other areas that may be considered in any of these functional deficits include the cerebellum, hippocampus, and the brain stem.

**Investigative Techniques**

Various investigative techniques have been employed in the study of the neuroanatomical and functional differences in individuals with ASD. Computed tomography (CT) offers a relatively inexpensive method of identifying intracranial masses, ventricular involvement, bleeding, and bony structural lesions. The usual technology behind tomography is x-ray, although other types may be used such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Unfortunately, the resolution is such that quantifying sizes of specific regional volumes is challenging if at all possible, and repeated exposure to ionizing radiation raises ethical dilemmas. Studies using CT have often ended up using qualitative measures rather than quantitative. PET and SPECT can be used in functional neuroimaging, albeit with the use of radiotracers.

MRI is reportedly a safer technique that greatly reduces radiation exposure, and can achieve much higher imaging resolutions. This is due to the fact that MRI is based on the absorption and emission of energy in the radio frequency spectrum generated by an atomic property known as spin. By selecting for specific processes, the “contrast” can also be adjusted (i.e. T1-weighted image versus T2-weighted image). The reduced radiation and increased resolution are helpful in studies, which involve multiple scans in younger individuals and examine structural differences. MRI is also more capable of making volumetric measurements, which allows for the comparison of structural differences in size of specific anatomical regions. Differences in size likely correlate with neural density. When measuring water molecule diffusion patterns, diffusion MRI [including both diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI)] can help identify neuronal fiber tracts that can infer connectivity in the brain. Limitations in the use of MRI include the presence of certain implants, pacemakers, or other ferromagnetic foreign bodies. There has been some thought that MRI may cause DNA breakage, but the long term harm of this has yet to be demonstrated. The majority of the studies discussed here use some form of MRI imaging.

Functional MRI (fMRI) attempts to represent neurological functioning by detecting changes in blood circulation in the brain. The underlying principle is that active areas of the brain are coupled with increased blood flow, and by detecting the difference between oxygen-rich and oxygen-poor blood, a map of brain activity can be made. Unlike PET or SPECT, it does not require exposure to radiation, or the injection or ingestion of tracing substances, many of which are radioactive.

Lastly, post-mortem studies have been used to identify gross structural differences, but are more useful when employed to help identify differences at the tissue level. This can include measuring cell densities, cell type distribution, orientation and structure. These may, in turn, be connected to molecular genetic processes that allow for greater understanding of the neurodevelopmental process of ASD. The primary challenge with this investigative technique is the availability of appropriate tissue samples along with those of matched controls.

**Total Brain Volume**

One of the most consistent findings among the papers reviewed here is that in younger individuals with ASD, a larger head circumference can be found. This has often been used as a correlate for total brain volume. One of the earliest reports of increased head circumference was made by Kanner in his seminal 1943 paper that described children with autism. Most studies consider children from about 1 year to 5 years of age.
Subsequent studies over the past 60 years have generally supported this finding\textsuperscript{9-14}. Overall, these papers reported that approximately 20% of autistic individuals in that age group had a head circumference greater than the 98\textsuperscript{th} percentile.

This appears to correlate with a 2008 review by Amaral et al., in which it was found that in very young children (ages 18 months to 4 years old), about 5-10\% had abnormal enlargement in total brain volume\textsuperscript{15}. This early growth trajectory is also supported by the findings of Shen et al. of significantly larger total cerebral volumes as early as 12 months of age and 18-24 months of age\textsuperscript{16}. Courchesne et al. reported that among boys aged 2-4 years old, 90\% of those with autism had a larger total brain volume\textsuperscript{17}. There are other studies that do not appear to support the finding of increased volume in younger individuals. A recent paper by Raznahan et al. suggests that some of the difference may be the result of using control data from commonly referenced databases rather than a community-based matched control set\textsuperscript{18}. They suggested that studies that used community-based controls were less likely to find a significant difference.

In older individuals, the findings seem to indicate that there may be no difference or even reduced volumes, which may support the idea that there is a flattening or even reduction in growth rate after the age of 4 or 5 years old\textsuperscript{19,20}. McAlonan et al. found that there was no significant difference in brain volumes for participants at 11 and 12 years of age\textsuperscript{21}. A longitudinal study also found no difference in total brain volumes between a sample of males with autism and an age- and gender-matched control group at both baseline and at follow-up (ages 8 years old and 12 years old respectively). This seems to indicate that over the first four years of life, there is rapid growth and that the next four years seems to bring this parameter back into the normal range.

**Grey Matter and White Matter Abnormalities in the Frontal, Parietal and Temporal Lobes**

Cody et al. reported on studies that suggested significant enlargement of the temporal, parietal and occipital lobes, but no differences in the frontal lobe in subjects with ASD compared to controls\textsuperscript{22}. A later review by Amaral et al. reported consistent volume increases in the frontal lobe, although with no particular pattern of regional specificity\textsuperscript{15}. When attempting to determine the underlying pathology for the increased volume in the various lobes, the findings are not consistent. In general, the increased volume is not necessarily consistent and/or proportional across the various cortical regions of the brain (e.g., orbitofrontal, parietal, temporal, etc.), or across grey matter/white matter/cerebrospinal fluid volumes.

It has been suggested that the increased volume may be better accounted for by increased white matter and not grey matter, at least in early childhood\textsuperscript{15,23}. Studies including older children do not appear to show this same relationship, and may actually show increased grey matter volume\textsuperscript{15}.

Chen et al. grouped findings of grey matter and white matter changes by volume and density\textsuperscript{24}. They noticed that with respect to grey matter volume, there were increases in the frontal, temporal and parietal lobes; however, when it came to studies measuring grey matter density, there was evidence of decreased density in the frontal and temporal lobes. White matter volume was decreased in frontal and temporal lobes and decreased in terms of density in the temporal lobe as well.

Both grey and white matter variations have been described as having a regional distribution. Grey matter was increased in the medial orbital frontal gyrus, and in the middle frontal gyrus, and found to be decreased in the pre- and post-central gyri of subjects with ASD\textsuperscript{25}. This contrasts somewhat with the findings described by McAlonan et al. where deficits were noted in the orbital, inferior and middle frontal gyri\textsuperscript{21}. A 2004 review reported grey matter deficits in the frontal-striatal region and white matter deficits in the left hemisphere\textsuperscript{26}. There appear to be age-based differences as well, which may go along with the observation that total brain volume “normalizes” in older children\textsuperscript{26}. Cortical thickness studies help to better characterize volumetric variations, and may reflect developmental dendritic branching.
and pruning\textsuperscript{23-25,27}. Unfortunately, there does not yet appear to be a consistent approach to defining the regions involved, and this may also help explain the variations noted.

**Cerebrospinal Fluid**

There do not appear to be many studies that measure the volume of cerebrospinal fluid (CSF) in subjects with ASD. The limited findings appear to show fairly normal fourth ventricle volumes. In another study, increased volume of extra-axial fluid was found in the ASD group for individuals between 6 to 24 months, and was estimated to be between 20\% and 33\% greater than in individuals without ASD\textsuperscript{16}. The amount of extra volume appeared to be correlated with later autism severity. Larger ventricle sizes were also found in the ASD group after controlling for age, gender, and total cerebral volume. McAlonan et al. reported that total CSF volume appeared increased in individuals with autism\textsuperscript{21}.

**Cerebellum**

Early post-mortem studies have suggested that abnormalities in the cerebellum may be related to autism. Differences have been reported in both the cerebellar cortex and the cerebellar vermis. Hypoplasia of the vermis appears to be the most common finding, and some studies postulate that this finding is in some way connected to cognitive ability. Other studies have found that there is an increase in cerebellar volume that is proportionate to the increase in total brain volume\textsuperscript{15,22}. One study that examined the cerebellum in a population under the age of 3 did not find a difference\textsuperscript{29}, which may indicate that the enlargement happens as the individual gets older (as opposed to the decreased rate of growth in the total brain volume). The finding of an enlarged cerebellum appears to persist into adulthood\textsuperscript{29,30}. In contrast to this, Allen and Courchesne found that the cerebellum was smaller (although the decrease was not statistically significant) in the autistic group, when examined in an adult population\textsuperscript{31}.

When characterizing the grey matter/white matter makeup, it has been reported that white matter volume is decreased in the anterior cerebellum and in the cerebellar tracts\textsuperscript{25,32}. A post-mortem study reported a decreased density of Purkinje cells, but this was confounded by the presence of co-morbidities such as epilepsy and intellectual disability\textsuperscript{15}.

**Basal Ganglia and Other Proximal Structures**

The basal ganglia are made up of several components including the striatum (caudate nucleus and putamen), the globus pallidus, the substantia nigra, the nucleus accumbens and the subthalamic nucleus. This is a region of interconnectivity to other parts of the brain, and like other “higher” level brain regions, appears to be associated with ASD.

In 1999, Sears et al. published findings from two studies involving adults that postulated that enlargement in caudate nuclei volume was associated with the ritualistic-repetitive, complex motor symptoms associated with ASD\textsuperscript{33}. This was based on the premise that the basal ganglia are implicated in OCD and Tourette’s disorder, which share similar motor features. Enlargement appeared to be proportional to the enlargement in total brain volume. They did not find any statistically significant differences in volumes for the globus pallidus or putamen. Herbert et al. studied the volumes in a population of young boys (ages 7 - 11) and found no differences in caudate nuclei volume, but increases in the globus pallidus and putamen\textsuperscript{34}. Subsequent studies involving both adolescents and adults seem to correlate better with the findings from Sears et al.\textsuperscript{4,33}. This may point to ongoing developmental variation that may be somewhat age-dependent.

Because of its role in social behavior and cognition, the amygdala has also been investigated. As in studies on other structures, younger children appeared to have an enlarged amygdala volume. Once again, other results are inconsistent, but volume may be related to age, gender, and even autism severity. Studies involving
older children and adults did not demonstrate between-group differences.\textsuperscript{4,15} There also appeared to be variations in grey matter tissue volume from anterior (reduced) to posterior (increased) amygdala.\textsuperscript{22} These findings may have to do with the degree of incomplete neuronal pruning. It has also been found that the increase was proportional to the increase in total brain volume.\textsuperscript{26} In studies where a smaller amygdala volume was found, it was correlated with post-mortem findings of increased cell packing density and truncated dendritic development.\textsuperscript{35}

There are limited studies involving the thalamus, cingulate cortex, hippocampus, and corpus callosum.\textsuperscript{15,26} Piven et al. originally described decreased corpus callosal volumes in those with ASD.\textsuperscript{29} In a more recent study, Prigge et al. found that increased corpus callosal area correlated with reduced severity of autism behaviors, higher intelligence, and faster speed of processing.\textsuperscript{36}

**Brief Summary of Functional Studies**

Given the variations noted in structural analysis, it is not difficult to see how connectivity between regions can be affected. More recent studies using DTI, fMRI and/or other network analyses have shown disruptions in communication tracts. Zielinski et al. found significant network abnormalities (in terms of spatiality and connectivity) between those with autism and controls.\textsuperscript{37} Other “network” studies have found abnormal patterns in the activation of mirror neurons, noting activity in the medial prefrontal cortex, superior temporal sulcus and right temporal pole of subjects with ASD.\textsuperscript{38}

Ecker et al. found that there are significant differences in the intrinsic organization of the brain in those with ASD.\textsuperscript{39} They suggest that there are molecular and genetic mechanisms that underlie the “atypical expansion and wiring of the cortex”.

Other recent investigations have attempted to correlate specific social cognitive tasks, language dysfunction, and tasks of executive dysfunction.\textsuperscript{4} These investigations have tried to measure hyper- and hypo-activation of relevant regions. Variation appears to be more pronounced in younger children with ASD than in adults with ASD.\textsuperscript{40} Further investigations in these areas may help characterize the developmental shifts over time in those with ASD.

**CONCLUSIONS**

The last 25 years have seen significant research into attempting to understand the etiology of autism. Many of the symptoms expressed by those with autism can be correlated to specific regions of the brain, and it is possible that by investigating these neuroanatomical structures, one can better understand the presentation. More recent investigations have attempted to better understand the dysfunction in the neural networks of those with ASD. Abnormalities have been reported in terms of both structure and function. Unfortunately, due to the heterogeneous presentation of those with ASD, consistent findings are not easily available. This is further complicated by the fact that the human brain continues to develop as individual’s age. Predicting the direction of this development is challenging, and numerous molecular and genetic processes underlie this progression. Further investigation of these underlying processes will be needed to advance our understanding of ASD and its related disorders.

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