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Enigma of the Developmental Causes in Individuals with Autism Spectrum Disorder

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ABSTRACT

Autism Spectrum Disorder (ASD) is a neurobiological developmental condition that can impact communication, sensory processing, and social interaction. ASD) is a developmental disability that can cause significant social, communication and behavioral challenges. For a long time now, the scientific community has been grappling with the enigma of what causes the developmental deficits in people on the autism spectrum, the causes of the ASD symptoms, and the timing of the manifestation of ASD in infants that occurs on or after 6 months. Several research studies show that the main cause of autism appears on account of the enlargement of the brain, specifically the amygdala, which could lead to communication and physical deficits, as well as sensory and light sensitivity. The research on the causes for ASD is still at the nascent stage as there are still many unanswered questions including about the causes of ASD. It appears that few if any ASD Research studies have a representative sampling for gender and the majority of research focuses on male individuals with ASD. This literature review reveals that more research is required to bridge the gaps in our understanding of ASD. The enigma of the developmental causes in individuals with autism spectrum disorder continues to be of interest to the scientific community and there is potential for further research regarding factors for pre-onset of ASD.

Introduction

The medical community has defined autism spectrum disorder (ASD) as a neurobiological developmental condition that can impact communication, sensory processing, and social interaction. The Centers for Disease Control and Prevention (CDC) report in 2021 found that, among 8-year-old children, one in 54 are autistic **[11]**. Several research studies have looked deeply into what could be causing these neurological challenges, but there have been no conclusive contributing factors correlating the causes of ASD. Autism spectrum disorder (ASD) is a developmental disability that can cause significant social, communication and behavioral challenges, and there has always been the question of what causes ASD symptoms. Researchers have theorized that some potential contributing factors could be brain enlargement or genetics that potentially lead to developmental neural deficits such as abnormal visual sensitivity, language processing, delayed auditory brainstem response, and challenges to physical activity. To date, all scientific research studies are post-onset of autism to look for contributing factors with no definitive pre onset indicators. Studies have shown that infants displayed no ASD symptoms for the first 6 months and signs of autism manifest between 6 and 24 months with no precise reason for the cause. The onset of ASD in infants continues to baffle the scientific community as more extensive research would be needed to determine if there are any pre-onset indicators. **[8,9]** The enigma of the developmental causes in individuals with ASD needs more research as currently there are gaps in understanding the contributing factors leading to the deficits.

Early signs and Diagnosis of ASD

The Amygdala has a primary role in the processing of memory, decision making, and emotional responses including fear, anxiety, and aggression. A 2022 research study by Shen et al. examined evidence of age and disorder specific trajectories in infancy to the enlargement of amygdala. **[1]** Previous research has demonstrated that the amygdala is enlarged in children with autism spectrum disorder (ASD). The precise onset of this enlargement during infancy, how it relates to later diagnostic autistic behaviors, whether the timing of enlargement in infancy is specific to the amygdala enlargement, and whether it is specific to ASD –or present in other neurodevelopmental disorders, such as fragile X syndrome – are not currently well known.

The researchers obtained MRIs of the 29 infants from ages 6-24 months with fragile X syndrome, 58 infants that had a high likelihood to be diagnosed with ASD who were later diagnosed with ASD, 212 high-likelihood infants not diagnosed with ASD, and 109 control infants with a total of 1,099 total scans. They found that infants who developed ASD had normal sized amygdala volumes at 6 months but had a higher amygdala growth between 6 and 24 months. By 12 months the ASD group had a significantly larger amygdala volume compared to all other groups. They found that the amygdala growth rate between 6 and 12 months was associated with greater social deficits in ASD children. **[1]** The Shen et al. study found that increased amygdala growth rate between 6 and 12 months occurs prior to social deficits and well before diagnosis. Many behavioral characteristics of ASD are indistinguishable at 6 months between infants later diagnosed with ASD and those with neurotypical development which makes it challenging to identify the ASD markers.

A similar study conducted in 2003 by Courchesne, Carper and Akshnoomoff on the brain overgrowth in the first year of life in autism found that there are at least 4 phases of brain growth in autism. **[3]** The study interestingly looked at Head Circumference (HC) at birth to be an early indicator of autism. **[10]** The first phase at birth showed that the average HC measurement is at the 25th percentile but was not accompanied by a decrease in prenatal body growth as the body length and weight at birth are not less than the values of healthy infants at birth. The study also found that brain volume decreases at birth appeared to be small and could not be used as a pre-onset indicator of autism in later years. However, the second brain growth phase involved a rapid and large brain overgrowth within the first year of infancy. The third phase lasted between 2 to 4 years with slowing in brain growth, but by 4 to 5 years of age the brain size reached the maximum size like what we see in healthy children, but 8 years too soon. The fourth phase involved gradual decline in overall brain size from middle or late childhood to adulthood. For this reason, early researchers were baffled as the size of the autistic brain appeared to be the same as normal healthy brain by adolescence or adulthood. The study had looked at the MRI of 8 to 48-year-old people with autism and healthy individuals and found that the brain of people with autism is only slightly larger than the average healthy size by late childhood, and that by adolescence and adulthood, there was no significant difference in size. They found that only during the first years of the postnatal life in autism, the brain is abnormally enlarged and not at birth or in later years (adolescence and adulthood). The clinical onset of autism appears to be preceded by 2 phases of brain growth abnormality: a reduced head size at birth and a sudden and excessive increase in head size between 1 to 2 months and 6 to 14 months. The study concluded that the abnormally accelerated rate of growth may serve as an early warning signal of risk for autism. This seems to support the theory that neural defects causing autism are happening prior to birth but there is still no evidence as to what causes ASD or when is the precise onset of ASD in the womb.

A different study conducted in 2023, much like the 2003 study, found that doing more profiling and research into X chromosomes may help in identifying the causes of neurodivergent disorders and identifying other X-linked disorders. **[10]** This study suggests that there's an age and disorder-specific pattern in how a brain develops and changes which cause autism, although this study does not confirm whether it's specific to ASD or present in other neurodevelopmental disorders, even though that would be consistent with previous research.

Research shows that people diagnosed with ASD have a slower response to sound than neurotypical children and adults. **[7]** A 2021 Miron study on Auditory Brainstem Response (ABR) in universal hearing screening of newborns suggests that this could be an early indicator of ASD. The study found that children with ASD, in comparison

to children without ASD, have low responses to sounds. They also identified that wave phase increases and latency prolongation in ABRs of newborn children who were later diagnosed with ASD were uniquely pronounced in the right ear. The negative V wave (5th sound wave) is prolonged in the right ear of ASD individuals and could be an early biomarker for ASD. This study has limitations as it is not very clear if individuals who developed ASD later in life would have failed the ABR test at birth. The ABR test could be an early predictor of ASD – with modifications to use high intensity sound – and could be considered a landmark breakthrough that would still require further research. **[7]** Brain enlargement and ABR have been shown to be early biomarkers for ASD diagnosis, however, there is still no causal factor associated with ASD diagnosis and is largely hypothesized to be genetic or environmental factors.

Developmental Deficits in ASD Individuals

ASD diagnosis largely appears to hinge on the manifestation of other development deficits. ASD individuals experience a variety of developmental deficits which tend to be the most noticeable part of autism. Neural deficits that exhibit in ASD individuals include language impairment, sensory issues with motion and light sensitivity, and decreased physical activity. It appears that most studies that looked at the developmental deficits were predicated on some brain abnormality, as the brain controls most of these functions.

A 2023 Arutiunian, V., Gomozova, M., Minnigulova et al study on structural brain abnormalities and association of language impairment in school aged children with ASD found that children with ASD had a " high variability in both non-verbal IQ (from very low, IQ = 40, to normal, IQ = 118) and language abilities (from non-verbal / minimally verbal to normal), whereas in TD (Typical Development) group of children there was much less variability. **[5]** According to behavioral assessment of non-verbal IQ and language, all TD children were within the normal range.". **[5]** The study **had** a total of 36 right-handed native Russian speaking children: 18 male children with ASD and 18 male children with TD (control group) with normal hearing and corrected-to-normal vision. The study used MRI and CAT scans to get brain images and cerebrospinal fluid was sampled in all participants. The review of the brain gray matter, white matter and cerebrospinal fluid analysis revealed that neither children with autism or the ones with TD had much variance in white matter or cerebrospinal fluid, but the ones with autism had a decreased gray matter. It was deduced that the greater the language impairment in autistic children, the variance in gray matter was higher than the TD control group. This lead to the conclusion that gray matter thickness could be a potential predictor of autistic language ability. It should be noted that this study had no female participants in either the control or ASD groups.

The Miron 2021 study showed that individuals with ASD had a slower response to sound and in many instances, were sensitive to sound intensity. **[7]** Motion sensitivity requires neural processing mechanisms of varying complexity. A 2003 study on motion perception and autistic individuals show that individuals with autism and normal intelligence process motion stimuli differently. The study used 12 autistic and 12 non autistic subjects to test and found that motion sensitivity of observers with autism is similar to that of non-autistic observers for different types of first-order (luminance with noise patterns) motion stimuli, but significantly decreased for the same types of second-order (texture with noise patterns) stimuli. Participants in the study had to view a display on a monitor and were subjected to light and motion stimuli sensitivity tests. The study concluded that ASD individuals process motion stimuli that require additional neural processing less efficiently than the control group (TD) due to less efficient integrative functioning of neural mechanisms at a perceptual level. The results indicated that neural processing deficiencies are evident in ASD individuals as they may have less visual-perceptual processing capabilities. **[6]**

Another developmental deficit that many ASD individuals face is their inability to participate in physical and play activities. In a 2015 study by Memari, A. H., Panahi, N., Ranjbar, E., Moshayedi, P et al on the patterns of participation of daily physical and play activities in children with ASD **[2]**, the researchers concluded that children with ASD tend to not have the same amount of physical activity (PA) as children without ASD do. This study was conducted with a sample of 53 male and 31 female children with high functioning ASD in the age range of 6 - 15 years old. To measure their physical activity, they used a checklist questionnaire known as the Godin-Leisure Time

Exercise Questionnaire (GLTEQ) and questioned the child's parents or guardians. The results of this study found that only 12% of the children with ASD that they gathered data on were physically active and 88% of the children with ASD were not physically active. ASD indicates several neurodevelopmental impairments which may end in impairments in motor or physical activities. The researchers examined that children with ASD tend to not have the normal amount of physical activity (PA) as kids without ASD do. The study states that barriers to PA could be because of the fact that they tend to have many behavioral indicators, more supervision from parents in comparison to children without ASD, lack of basic skills, exclusion from other children, or even unsafe equipment **[2]** The contributing factors for the language impairment, slowness in responding to sound in ASD individuals and motion sensitivity perception remain unexplored even though all this appears to tie back to brain developmental deficits. The developmental deficiencies also manifest in lower physical activity in children with autism.

Gap in ASD Research Studies

There exists a significant research gap in understanding sex and gender effects in the ASD individuals. The ASD studies thus far have no commonality or convergence of symptoms in male ASD and female ASD individuals. There is insufficient statistical power to detect significant sex/gender-by-diagnosis interaction effects or might be at risk of reporting false-positive findings or generalization of results being made applicable to both genders. Additionally, there is a significant under recognition of ASD in females, meaning most studies concentrated on the male-based understanding of ASD. The under recognition of ASD continues as it relates to behavioral markers, the differences in manifestation in male and female and very little has been done to include females in the sampling of ASD research. **[4]** This is a very large knowledge gap in what we know about gender/sex differences in human autistic brains and future research should include sex and gender sampling to gain a more inclusive, better analysis and understanding of the effects of ASD on the sexes.

Conclusion

ASD is a neurobiological developmental condition that is in the nascent stages of research and diagnosis. Various studies on the contributing factors for ASD have yielded no conclusive result. All research studies appear to be post-ASD diagnosis and check for correlation between the ASD diagnosis and the neural deficiencies. The head circumference (HC) measurement at birth could potentially be used as an early indicator of future onset of autism symptoms but there is no research data on what is causing this in the womb or the precise onset of this decrease in HC. The onset of autism symptoms appears to be evident only after 6 months of birth which makes it challenging to diagnose the contributing factors causing the disorder. Even though one conclusive contributing factor appears to be the enlargement of the amygdala in autistic individuals, it is still not clear what is causing this abnormal brain enlargement leading to the disorder. The sensory, language, and social deficits leading to developmental deficiencies can be linked to the neural deficits which could potentially be on account of the brain overgrowth. Further research is needed in this field to provide any conclusive evidence. Also, it appears that all ASD Research studies do not have a representative sampling for gender/sex and is skewed toward male ASD individuals. This literature review reveals that we need more research to bridge the gaps in the ASD study for a better understanding of the disorder and what the directions scientific community needs pursue in the future.

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