EVALUATION OF THE BRAIN STEM USING MAGNETIC RESONANCE IMAGING HISTOGRAM ANALYSIS IN ASD

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Abstract

A neurodevelopmental illness called ASD affects roughly 1 in every 60 American kids. ASD is thought to involve the cerebral cortex and cerebellum, although our knowledge of the brainstem's function in ASD in young children is still in its infancy. Given the high correlation between ASD and brainstem pathology in terms of sensory and motor symptoms, it is vital to understand the role of brainstem neurotransmission in ASD. Since the brainstem seems to play a significant role in ASD, this review sought to synthesize data from a variety of sources. Examining the data through the lens of hierarchical brain development allowed us to gain a deeper understanding of ASD as a neurodevelopmental condition. This assessment of the research suggests that, given what we know now, developmental abnormalities in the brainstem might have knock-on effects on cortical and cerebellar formation, which in turn might induce ASD symptoms. Both epidemiological studies in humans and animal models of autism reveal a possible association between defects in brainstem substructure development, namely during the maturation of the brainstem's monoaminergic centers, and ASD or autism-like behaviors. Evidence from human histology, psychophysiology, and neuroimaging is also discussed that suggests aberrant brainstem development and maturation in ASD may be associated to significant ASD symptoms such sensorimotor features and social reactivity. It is evident from this analysis that more research is needed to validate the early identification of brainstem-based somatosensory and psychophysiological activities that occur in infancy, and to examine the brainstem across the lifetime while taking age into account. It is clear that earlier diagnosis and better therapy for ASD might be achieved with more awareness of the brainstem's role in the disorder, although this study is still in its infancy.

1. INTRODUCTION

ASD is a lifelong condition with no known treatment that affects 1 in 60 children. This condition, the origins of which may be traced back to the maturation of the brain, manifests itself in a variety of ways in various patients. Human genetics and animal model research have both shown that ASD characteristics may originate in early-life neurodevelopmental problems. The brainstem, the youngest and most immature region of the brain, may be at the root of problems with social communication, confined, repetitive behaviors, and co-occurring sensory impairments. The first theory of ASD to focus on the brain focused on the brainstem, suggesting that anomalies in this part of the brain's early neuronal development were responsible for ASD symptoms. New evidence supports the neurodevelopmental theory of autism and highlights the importance of the brainstem in autistic behaviors, suggesting a connection between pons hypoplasia and ASD symptoms. Even with these brainstem-based ideas, however, the brainstem has gotten remarkably little attention in ASD research, making it hard to establish a causal relationship between ASD symptoms and brainstem function. The scant body of research can be traced back to problems with conceptualization and methodological uncertainty. Basic diagnostic signs of ASD have been theoretically connected to higher order cognitive skills including language and social motivation. Because these cognitive domains are likely supported by elements of the cortex, it has been studied more frequently than deep brain areas like the brainstem. Due to its small size, functional diversity, and anatomical complexity, studying the brainstem in vivo involves methodological obstacles. Recent technological developments are beginning to reduce the methodological challenges of magnetic resonance imaging (MRI) of the brainstem, although it has not yet been applied to the study of ASD. However, these conceptual and methodological issues may have limited our knowledge of the brainstem's role in ASD, despite the fact that the few studies that have investigated the brainstem in ASD give strong support for its critical function during the neurological unfolding of autism. If researchers consider the notion that autistic symptoms originate in abnormal brainstem development, they may be able to gain a mechanistic understanding of the neurological underpinnings of ASD and locate behaviors and biomarkers that permit earlier diagnosis. Signs of autism that can be used to diagnose the disorder often appear between 23 and 33 months of age, after brainstem development has largely concluded. Since behavioral diagnoses can be made at far younger ages than the brainstem matures, a
neurodevelopmental cascade that begins in the brainstem and culminates in the presentation of core symptoms may go unnoticed. On the other hand, there is growing evidence connecting ASD with improper brainstem development. This information comes from many different areas of neuroscience, including as developmental biology and psychophysiology, as well as studies involving humans and animals. No comprehensive summary of these disparate data sets exists. Therefore, the purpose of this study was to investigate the involvement of the brainstem in ASD by integrating findings from a variety of areas. The aim of our study was to examine the data through the lens of hierarchical brain development, which emphasizes the important role of the brainstem as a guide during neurodevelopment and is thus relevant to ASD as a neurodevelopmental disorder. For this reason, we will first provide a brief summary of the functions of the brainstem that are crucial throughout early brain development, and then we will zero in on the ASD-related behavioral features that may be indicative of abnormal brainstem maturation. We next emphasize the most critical areas where more research is needed after summarizing the existing facts for the brainstem's role in ASD.

2. BRAIN STEM EVALUATION AND ANATOMY

2.1 Brainstem anatomy's complexity

The brainstem is essential to organismal existence because it facilitates fundamental physiologic and behavioral processes. Brainstem neurotransmission is essential for a wide variety of biological processes, including breathing, heart rate, stress response, gastrointestinal management, and basic visual and auditory processing. The brainstem is an exceptionally conserved part of the vertebrate brain because of its vitality and adaptability. The organization of the brainstem is exceptionally complicated, which may be due to the brainstem's critical purpose, which has been maintained across developing phylogeny. This structure, which arises at the same time as the closure of the neural tube but unlike many others in the brain, does not give rise to other regions. On the other hand, the brainstem's three major sections are each composed of several smaller structures. The neuronal cell bodies, housed in gray matter nuclei, are dispersed throughout the brain's intricately interwoven white matter tracts, each of which has its own distinctive presentation, such as the reticular formation's gray-white matter mesh or the inferior olivary nucleus's flower-like substructure.

Fig 1. Anatomic view of Brainstem

2.2 Brainstem and hierarchical brain development

The brainstem's importance in development must be appreciated if researchers are to get insight into the possible significance of this brain region in the development of ASD symptoms. Despite the fact that the brain neither develops nor functions in isolation, conventional ideas of autism diagnosis have centered on anomalies in the cortex. When the brain is developing in the womb, it uses older, more primitive brain structures as a sort of hierarchical framework to guide the formation of newer, more advanced brain regions. It is thought that signals from the inferior olive and pontine nuclei of the brainstem, via mossy and ascending fibers, contribute in the development of the cerebellum. Because of these processes, we have an integrative brain, in
which the form and function of the more complex cortical circuits rely on the precision of the underlying neuronal circuitry that evolved in our ancestors' brains. The integrity of the brain's lower-level processing can be affected by even a slight perturbation in the early stages of neurodevelopment, with negative effects propagating to the brain's higher-order neurocircuitry. The brainstem is well-positioned to play a key role in the establishment of mammalian brain hierarchy, suggesting that it is involved in all mammalian brain processes, even those that have traditionally been associated with higher-order circuitry. If the brainstem wiring is not properly established, then defects within the brain circuitry of organisms that are relatively recent in evolutionary terms could give rise to a spectrum of abnormal behaviors. For this reason, we will be focusing on the following three processes to illustrate the basic role of the brainstem in neurodevelopment:

- activating neurons at a young age and encouraging mature brain circuitry is crucial for later-stage brain development.

Animal models have been used extensively to study the mechanisms behind these developmental processes, and because to a high degree of evolutionary conservation, we may use this information to learn more about human neurodevelopment. Studies in humans in the wild support these theoretical hypotheses, showing that the aforementioned mechanisms indeed characterize the physical and functional link in the brain. Atypical behaviors may originate in the brainstem if it plays a critical role in neurocircuitry creation, which in turn may trigger a neurodevelopmental cascade leading to abnormal brain cytoarchitecture and connectivity. We provide a summary of the most relevant evidence supporting the hypothesis that the brainstem plays a pivotal role in early brain development. Critical to the initial steps in the development of the brain's neuroarchitecture, cell migration and differentiation are aided by the brainstem's monoaminergic circuitry. A variety of monoamines (including norepinephrine, dopamine, and serotonin) are secreted autocrinely from the brainstem to act as neurotrophins in the developing brain. The process of cortical layering, also known as lamination, is a major turning point in the evolution of the nervous system. The function and regional specialization of the brain are determined by this process, which is characterized by the fundamental neurodevelopmental processes of cell migration and differentiation. Norepinephrine has been shown to enhance neuronal migration and differentiation via influencing Cajal-Retzius cells in the brainstem. In addition, serotonin, a neurotrophin and trial neurotransmitter produced in the brainstem, promotes lamination during typical brain growth. The brainstem appears to have a foundational role in the establishment of the brain's hierarchical structure due to the importance of its neurocircuitry in the processes of neuronal migration and differentiation at an early stage of brain development.

Prior to the establishment of synaptic function, early neural activity appears to be crucial to the development of the brain's morphological and functional connectivity. When it comes to the molecular processes that allow pre-synaptic neuronal activation, the brainstem serotonergic system is one of the first and most significant actors. Neurons that begin their development in the first few weeks of pregnancy provide extensive coverage of the di- and telencephalon by the middle of pregnancy. For their part, growing cortical glutamatergic neurons eagerly soak up the released serotonin and put it to use in establishing a connection between the thalamus and the cortex. Early wiring of brainstem serotonergic projections is hypothesized to serve as a pattern for adult glutamatergic neurotransmission between the cerebrum and thalamus, suggesting a pivotal role for these projections in brain development. Also, it was shown that tonotopic structure of the entire auditory system, including the auditory cortex, is dependent on serotonin transmission in the brainstem, which controls early neuronal activity in the brainstem and the midbrain. Early neuronal activity in the brainstem primes the developing auditory system to receive sensory-evoked impulses, lending credence to the theory that the brainstem plays a critical part in the neurodevelopmental process.

2.3 Establishing neuro architecture

The monoaminergic circuitry in the brainstem plays a critical role in enabling cell migration and differentiation during early development, two events that are critical in the construction of the brain's neuroarchitecture. Some of the most important neurotrophins for brain development are the monoamines norepinephrine, dopamine, and serotonin, all of which are secreted in an autocrine fashion from the brainstem. This process of cortical layering, also known as lamination, represents a watershed moment in the evolution of the nervous system. The fundamental neurodevelopmental processes of cell migration and differentiation characterize this procedure, and they are responsible for determining the brain's specialized functions and anatomical locations. Norepinephrine has been shown to enhance neuronal migration and differentiation by acting on Cajal-Retzius cells in the brainstem. Additionally, serotonin, a neurotrophin and trial neurotransmitter produced in the brainstem, promotes lamination during typical brain growth. Emerging evidence indicates that the brainstem plays a critical role in the migration and differentiation of neurons beginning at a very young age, laying the groundwork for later, higher-order brain development. Presynaptic activity appears to play a significant role in the development of both structural and functional synapses in the brain. When it comes to the molecular processes that allow pre-synaptic neuronal activation, the serotonergic system of the brainstem is one of the first and most significant actors. Beginning in the first trimester of pregnancy, serotonergic neurons give extensive innervation to the developing diencephalon and telencephalon. When serotonin is released, it is quickly
taken up by newly created glutamatergic neurons in the cortical regions, which use it as a "trial" neurotransmitter on their way to establishing a connection with the thalamus. Brainstem serotonergic projections have been shown to play a crucial role in laying the framework for mature glutamatergic neurotransmission between the cerebral cortex and the thalamus. It was also discovered that serotonin signaling in the brainstem acts as a map for the development of early neuronal activity in the brainstem and midbrain, regions that play a pivotal role in the tonotopic structure of the entire auditory system, including the auditory cortex. The hypothesis that the developing auditory system is primed by early neuronal activity in the brainstem suggests that the brainstem may play a crucial role in the neurodevelopmental cascade. Myelination is a crucial step in the development of brain circuits, which involves a complex orchestration of events. Oligodendrocytes are a type of glial cell that myelinate axons to protect them from damage and facilitate rapid communication between neurons. Global brain myelination may have active requirements for early brainstem function. Alterations to the serotonergic pathway in the brainstem cause aberrant oligodendrocyte activity, which in turn alters brain myelination on a molecular level. The brainstem is the first part of the brain to be myelinated during pregnancy, following the hierarchical pattern seen throughout the body. The myelinated brainstem and the areas of the brain responsible for shaping the body in utero are among the first to develop. A system that matures early and completely is the human auditory system. Myelination initially appears in the auditory brainstem during 26 weeks of gestation, demonstrating the rapid development of this area. This means that the primary auditory cortex is the first part of the brain to undergo lamination, myelination, and activity. Moreover, the brainstem's central involvement in neurodevelopment is supported by the caudo-rostral maturation of brain neuronal circuitry.

All of this highlights the crucial role that brainstem circuits play in maintaining and guiding healthy brain growth. The potential significance of deep, ancestral brain structures like the brainstem to the pathophysiology of neurodevelopmental diseases is a core assumption of this form of "bottom-up" development. It is challenging to establish a direct link between early brainstem development and future ASD symptoms, despite the fact that the available evidence for neurobiological features of ASD suggests that at least some of the symptoms may be derived from brainstem-supported neurodevelopmental events. First, issues with neurotransmission in the brainstem during development may lead to aberrant cortical structure and connectivity, which may have consequences for lamination and areal specialization. People with ASD have been found to have a number of cortical atypicalities, both in terms of appearance and function. Second, as serotonin is essential for establishing thalamocortical link throughout development, serotonergic projections from the brainstem may be involved. Abnormalities in the anatomy and function of the connections between the thalamus and the cortex have been found in postmortem studies of people with ASD. The shape of serotonergic axons is one example of these anomalies. Finally, it is speculated that tuning of the auditory system occurs prior to the propagation of the first auditory signal through spontaneous activity in the brainstem. Many persons with ASD have abnormal auditory function, and the severity of autism seems to be connected with this. This may be the result of a disruption in the typical developmental trajectory. It comes to expect that the brainstem has a key role in the expression of ASD symptoms, given its prominence in hierarchical brain development.

3. HUMAN EVIDENCE OF BRAINSTEM'S CONTRIBUTION TO ASD

Human epidemiology lends credence to the idea that abnormal brainstem development plays a role in creating ASD symptoms. Epidemiological research has linked prenatal exposure to harmful environments to an increased risk of ASD. The absence of the forebrain and the rapid development of the brainstem during the first few weeks of embryonic development has been linked to the onset of ASD and other neurological disorders. In the first place, there was an association between valproic acid use in the first trimester of pregnancy and an elevated risk of ASD in the offspring. Crucially, among different exposure durations, the damage that occurred during rapid brainstem development was responsible for 100% of autism cases. Furthermore, antibodies given during gestation in rodents were the sole way to replicate ASD incidence, which is linked to an abnormal prenatal maternal immune response in humans, further implicating nervous system development in autism etiology. These epidemiological findings collectively suggest that environmental experiences related with the neuropathology of ASD may have happened during the era of active brainstem development, suggesting a possible relationship between early-life environmental insults and ASD susceptibility.

According to the hierarchy of brain development, the brainstem plays a pivotal function and may play a part in the development of neurological symptoms. Studies in preterm infants can help link atypicalities in infant behavior with aberrant brainstem development, despite the methodological difficulties of studying prenatal brain development in vivo in humans. Premature newborns are at risk for having an undeveloped brainstem since the brainstem completes its development between 35 and 37 weeks of gestation. Premature newborns have been demonstrated to have abnormalities in the autonomic processes that are supported by the brainstem. These include arousal, temperature control, breathing patterns, visceral homeostasis, and heart rate variability. Deregulation of neurologic activities, such as the auditory brainstem response, has been linked to brainstem...
dysfunction in the perinatal period, along with atypicalities in the autonomic nervous system. This millisecond sensitivity of ABR is what makes it such a great tool for non-invasively assessing brainstem function, as it allows for the dissection of neural responses from several brainstem substructures. Evidence from abnormalities in heart rate variability (HRV) and auditory brainstem response (ABR) in preterm children corroborate previous findings that neurological impairments in the brainstem are a common feature of premature birth. Given the brainstem's position in the neurodevelopmental hierarchy, premature infants who experience delays in this area's maturation may also be at risk for faulty development of higher-order brain regions, which would be manifested in later-observable behaviors.

Notably, children with ASD also revealed the same neurological dysfunctions situated in the brainstem as the pre-term babies.

Similarities in symptoms involving the brainstem suggest that abnormal brainstem development may play a role in the neuropathogenesis of ASD. The statistics lend credence to this theory by demonstrating that the prevalence of ASD increases with decreasing gestational age, making it more common in preterm infants compared to full-term children. Furthermore, the aberrant evolution of brainstem-based symptoms, such as HRV and ABR, suggest a role for the brainstem's developmental trajectory in ASD. Therefore, preterm children with appropriate neurodevelopment have normal HRV by the time they are toddlers, but children with ASD continue to have abnormal HRV throughout their lives.

It is possible that the severity with which the brainstem circuitry is changed in ASD is what causes the unusual neurodevelopmental trajectory seen in this disorder, as impaired HRV persists throughout time in individuals with ASD.

ASD may also be caused by atypical development of the brainstem, which would then affect the functioning of higher-order brain regions. For instance, abnormal ABR was linked to attention and sociability problems in children with ASD, providing a mechanistic explanation for the relationship between faulty brainstem neurophysiology and a central symptom category of autism, namely, social communication difficulties.

Recent discoveries in normally developing and autistic youngsters further highlight the connection between social function and brainstem neurocircuitry. Examples include pre-term infants with normal ABRs displaying abnormalities in social engagement that manifested as poor social attention by the age of 7-8. Concurrently, the severity of the fundamental autistic symptoms, such as social and language ability, may be predicted by an abnormal ABR in pre-term newborns who were later diagnosed with ASD. Nonetheless, in ASD, ABR shifts significantly over time. Recent meta-analysis suggests an extremely rapid developmental trajectory of ABR in ASD, with increased ABR latency in childhood with ASD changing into decreased ABR latency in adults. Given the quick age-related increase in ABR, it's possible that the neurobiology underlying ASD symptoms is particularly flexible at certain times, making timely therapies a real option. Longitudinal research on the age-related specificity of brainstem-based behaviors in ASD could one day reveal critical windows of opportunity for re-wiring developing neural circuitry through intervention.

Alterations to multisensory integration may also result from the disrupted brainstem development seen in ASD. Although MSI is a complicated function that relies on input from the cortex, it is shaped in the neonatal period by sensory input to the superior colliculus in the brainstem, including auditory, visual, and somatosensory signals. In particular, SC facilitates MSI through the "learning" to integrate multimodal sensory input during the prenatal period. According to ABR research, many infants who go on to acquire ASD showed signs of impaired auditory function during the perinatal era. Researchers found that audiovisual integration (MSI) was uncoupled from other forms of MSI when auditory function was disrupted in animal models of early infant development. Notably, children with ASD were found to have abnormalities in audiovisual integration, although these problems were not present in later life. Given that animal studies have shown that impaired audiovisual integration persists into adulthood if not addressed during the critical developmental period of heightened SC plasticity, the abnormal development of audiovisual integration in ASD is of particular relevance. The fact that children with ASD can make up for their impaired sensorimotor skills by reaching typically developing levels of audiovisual integration supports the presence of compensatory mechanisms. It is unclear how the brain's neurobiology adapts to such a developmental course: the SC's function may be reintegrated, new cortical areas may be recruited, the brainstem's neurocircuitry supporting incoming stimuli may be reshaped, or some other mix of these processes may be at work. There is debate as to whether or not the loss of higher order cognitive function that may result from compensatory mechanisms for early sensory deficiencies contributes to the core autistic symptoms of language impairment and abnormal social communication. The time course and appearance of ASD symptoms may be affected by early developing brain areas, such as the somatosensory cortex (SC), and studying the neurological basis of abnormal progression of audiovisual integration may shed light on this.
Recent research in high-risk infant siblings of children with ASD has shown that observable behavioral traits can be identified as early as infancy, and that these qualities may correlate with atypicalities in brainstem neurocircuitry. Children who were ultimately diagnosed with ASD showed a reduction in their visual attention to eyes between the ages of 2 and 6 months, according to a longitudinal study of newborns at high risk. Abnormal social information processing in newborns between the ages of 2 and 6 months old may have its origins in abnormal brainstem function, since this has been known for some time. The data showing asymmetric visual tracking in one-month-old infants with ASD provide more support for a brainstem involvement in the disorder. In addition to delayed motor performance at 7-10 months, early eye gaze function was also described, which is consistent with the seminal results that infants with ASD showed motor atypicalities at 4-6 months of age. Many lines of evidence have since converged to show that abnormal motor development within the first two years of life is associated with an eventual diagnosis of ASD. The results showed that the child displayed abnormal posture, abnormal spontaneous movement, irregular writhing and fidgeting, restricted gripping abilities, and a delay in completing the motor milestones, and/or an atypical presentation of those milestones. With a few notable exceptions, the growing body of research on motor problems in infants and young children with ASD suggests that this area of development may hold a diagnostic biomarker for the disorder. The developing brainstem is responsible for basic reflexes and spontaneous micro-movements in infants, while both the cortex and the subcortex are involved in supporting complex motor actions in adults. Importantly, basic reflexes and spontaneous micro-movements were shown to persist throughout infancy in ASD, supporting a role for the brainstem in the development and maintenance of ASD symptoms over the course of a person's lifetime. There was also a correlation between aberrant motor activities and the basic diagnostic criteria of ASD, both in infancy and later in life, which suggests a possible convergence of the two domains' underlying neurobiology. Since the motor atypicalities seen in ASD span such a broad spectrum of human motor function and are also seen in other developmental disorders, it may be possible to identify early behavioral markers specific to ASD by analyzing how and when the different motor modalities overlap with the core autism features. The question of whether or not the presence of motor difficulties predicts the severity of may be of particular relevance. The next step in elucidating the neurobiological foundation of ASD could be to evaluate how such baby motor activities are related to neonatal brain shape and function. To find the faulty brain regions that set off the improper neurodevelopmental processes that ultimately result in the core ASD symptoms, we need to know which neuronal pathways underlie early motor atypicalities in ASD. Considering the extraordinary degree of neuroplasticity in infancy, it may be possible to reroute the neuropathological development and prevent the appearance of the severe symptoms of ASD by identifying and intervening with early behavioral signs of ASD.

4. BRAINSTEM INVOLVEMENT IN ASDS: POSTMORTEM EVIDENCE

The neurobiological foundation of ASD symptoms is illuminated by both epidemiological and behavioral data, however these sources can only provide an approximation of the brain neurocircuitry implicated in the disorder. Histological evidence, on the other hand, gives concrete proof of tissue abnormalities without requiring any speculation regarding the sequence of events leading up to the diagnosis of autism. Despite its obvious relevance to autism, the brainstem is rarely examined in autopsies. We don't know as much as we'd want because of problems with the research methods or the scope of the question being asked. Histological evidence may not be conclusive, but it is compatible with evidence from behavioral and psychophysiological studies that point to a function for the brainstem in the development of ASD. Abnormalities in HRV and arousal states may be linked to ASD's underlying hyperactivity/hypoactivity, as the medullary arcuate nucleus mediates the equilibrium between the sympathetic and parasympathetic nervous systems. Individuals with autism may also experience motor and sensory problems due to a dysfunction in the inferior olivary nucleus (ION).

Eye staring is abnormal in ASD and may be utilized as an early indicator of autism; the ION and the olivofloccular system are involved in this behavior. It was also found that people with ASD have abnormalities in the superior olivary complex, which can range from a complete lack of the structure to one that gives the impression that it is still developing. Changes in neurotransmission in the SOC have been linked to autistic features like difficulty with frequency discrimination and abnormal ABRs in the auditory brainstem. Abnormal blood vessel maturation was seen in the brainstems of deceased people with autism. Since blood flow is directly related to neural activity, our results support previous histology evidence pointing to the brainstem as a potential contribution to ASD.

However, determining the specific significance of any one brainstem substructure has been challenging due to the great diversity of morphological changes associated with ASD. Despite this, there is agreement among the studies that particular deficits in the brainstem are present. Although the brainstem was not the only focus of the investigation, anomalies in its substructures were found in 6/6 cases with ASD. Such exploratory histology is helpful for locating potential new research directions; nevertheless, it needs to be followed by a study that zeroes in on the brainstem specifically. Thus, in the aforementioned
 exploratory work, five out of six brains provided adequate sections to examine ION; nevertheless, one of these five seems to have undergone severe postmortem degradation. Morphological ION abnormalities were found to be quite severe in three of the remaining four brains. These results provide strong evidence for the need for more histological studies of the brainstem and ASDs to uncover any additional links between these conditions. The heterogeneity of ASD may also account for the varying histology findings in the brainstem. One of the six brains described had an abnormal white matter tract in the pontine tegmentum, while another had abnormal structure in the facial and superior olivary nuclei. Even within the same area of the brainstem, histological abnormalities can take many forms. Individuals with ASD have been found to exhibit a number of SOC abnormalities, including underdevelopment, fewer and smaller neurons, aberrant geometric structure, and almost complete absence. Moreover, one cannot deny the significance of age. Another finding was that a 4-year-old child with ASD, but not an adult, had a smaller midbrain and a larger medulla. All things considered, the morphological data points to a role for the brainstem in autism. Furthermore, it emphasizes the histological variety of the neurological substrate of ASD, highlighting the significance of taking heterogeneity into consideration when studying the illness. Postmortem histology studies have indicated a role for the brainstem in ASD, albeit the exact nature of this role is still up for debate. The results of in vivo radiography investigations on the morphometric aspects of the brainstem in autism are inconsistent. Early neuroimaging showed a smaller midsagittal region of the brainstem in autistic persons, which is consistent with the discovery of a larger fourth ventricle in ASD. However, some studies have failed to detect any difference in posterior fossa planimetry between autistic and neurotypical participants. It’s possible that the small and varied samples employed in the first experiments led to such conflicting findings. Because ASD is characterized by such a broad spectrum of symptoms, it is challenging to find common neurological abnormalities among people with the illness. Importantly, studies showing aberrant brainstem morphometry in autism required either large sample sizes or tight inclusion criteria for people with ASD. As with the wide variety of tissue atypicalities found in the histology data, this discrepancy between early MRI findings may be explained by the high degree of heterogeneity associated with autism. The function of the brainstem in autism symptomatology may not be fully understood from group-to-group comparisons of physical morphology alone. By comparing brainstem size to the wide variety of symptoms experienced by patients with ASD, brainstem volume studies may provide further insight on the neurological basis of the disorder. According to the results of a large-scale structural MRI study, reduced brainstem volume is associated with aggression in ASD.

In addition, autistic boys have been demonstrated to have aberrant development of brainstem volume. This study adds to the growing body of evidence that highlights the issue of heterogeneity in autism by documenting a wide range of individual developmental characteristics. This difference in volume, however, was associated with distinctive sensorimotor styles, suggesting that it may not have resulted from random chance alone. Variations in brainstem gray matter volume were associated with variances in oral sensitivity, and brainstem white matter volume was associated with variations in motor skill. It is possible that critical brainstem features and their connection to ASD symptoms can be elucidated through study of tissue microstructure in addition to evaluating gross structural volumes. Since the brainstem plays such a vital role in relaying signals between the brain and the rest of the body, it stands to reason that neural impulses must successfully traverse the brainstem’s circuits in both directions for proper functioning. Health of neural circuits can be inferred with the help of diffusion tensor imaging (DTI), a method for evaluating the underlying architecture of brain tissue. A hallmark of autism spectrum disease is impaired social communication, which we have previously linked to variations in white matter architecture in the brainstem using DTI. Lower-level processing is expected to be incorporated in brain networks responsible for social interaction, expanding the view from the traditional one that only higher-level processing in the cortex is responsible for social communication. It is unclear what role the brainstem plays in higher-order brain activity, but our own study shows a relationship between microstructure in the brainstem and social communication symptoms in ASD. In individuals on the autism spectrum, there is a strong correlation between the microstructure of the brainstem and measures of grip strength, a lower-order motor ability. While this study did find a correlation between grip strength and social communication in ASD, it was shown to be statistically insignificant if brainstem microstructure was taken into account. Based on these findings, it appears that the brainstem may play a role in regulating both higher- and lower-level cognitive processes. Collection of information indicating a link between ASD and faulty cortical-brainstem connections. These functional connectivity results are in keeping with tractography research demonstrating an aberrant white matter link in ASD between the brainstem and cortical and subcortical regions. Taken together, these results suggest that a deficit in the brainstem’s ability to maintain top-down and bottom-up brain-body connection may be one of the most significant neurophysiological characteristics of ASD. Due to issues with scanner noise and the inability of many software packages to do brainstem investigations, neuroimaging studies aimed at elucidating the brainstem’s role in ASD are only getting off the ground. Although the brainstem has received little attention in the past, recent breakthroughs in neuroimaging techniques and encouraging early discoveries have generated renewed interest in this region.

Indeed, recent advances in brainstem MRI have enabled researchers to resolve several brainstem substructures in vivo in humans, permitting an in-depth examination of brainstem microstructure and its putative association with ASD symptoms. Non-invasive imaging techniques have advanced to the point where they can be used to study the growing brain all the way through pregnancy and into infancy, giving scientists a better chance of making the connection between abnormal brainstem
activity and an ASD diagnosis. Therefore, future research utilizing these novel approaches in early infancy and possibly in utero would allow for a more direct examination of whether brainstem development is relevant in ASD.

5. CONCLUSION AND FUTURE SCOPE

people have thought that different parts of the brain are to blame for ASD symptoms. Yet, deep parts of the brain like the brainstem have been ignored for a long time in the quest to figure out how the brain works in people with ASD. Aberrant brainstem neurotransmission, on the other hand, makes ASD symptoms worse. This is clear when the focus moves from the core of ASD to other symptoms, like sensory problems or unusual psychophysiological responses. The goal of this study was to take stock of what we know about the brainstem in ASD. It did this by drawing on a wide range of sources, from developmental biology to psychophysiology, and by using both human and animal models. Epidemiological statistics and psychophysiology have hinted at the role of the brainstem in ASD, but direct evidence from histology and neuroimaging studies is just starting to come in. But it’s hard to know the full extent of this participation because the results of behavioral and neurobiological studies don’t always match up. There are three main ways to find out if the symptoms of ASD are caused by a problem with how the brainstem works or not.

1. Group-differences study designs may not be the best way to study brainstem-based ASD symptoms because they can be different. Instead, we might look into the neurological causes of the wide range of symptoms seen across the autism spectrum.

2. To get rid of methodological differences, brainstem-related behaviors must be evaluated consistently and directly linked to brainstem differences using the best psychophysiology and/or neuroimaging methods.

3. we need animal models in which specific substructures of the brainstem can be changed to see if this causes ASD-like behaviors. This will help us figure out how the brainstem contributes to the neuropathogenesis of the disorder.

Based on what we’ve learned from this review, we’ve come up with a model of how the brainstem affects ASD symptoms. The basic sensorimotor symptoms of ASD may show up before the more complicated social communication and repetitive behavior symptoms. This is because early disturbances that affect the developing brainstem can have a cascade effect on the development of the brain and cerebellum. By the time the main symptoms show up, the brain as a whole has already changed to fit the abnormalities that were there from the start. People with ASD often have a wide range of symptoms because their genes and their environment interact with each other.

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