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Review Article

Neurological Profiles Associated with Autism Spectrum Condition

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ABSTRACT

Autism is understood to be a neurodevelopmental condition presenting with social difficulties, communication problems and repetitive behaviors or interests. Much research is now available, as diagnosis rates have increased nearly 800% in just 20 years, leading to an abundance of research. Even so, findings seem contradictory and confusing. It's hard to determine if anything of merit has yet been uncovered; autism therapy has shown subpar results and many autistic individuals struggle immensely when they reach adulthood and age out of services. Currently, autism is diagnosed by only behavioral criteria. If more was known about the neurodevelopmental trajectory of this condition, both diagnostic tests and therapy would be greatly improved.

This review analyzes existing research concerning the neurodevelopment of autistic individuals from infancy and genetic conditions that are known to be associated with autism. It found that there is not one autistic neurotype but four. Two profiles present with megalencephaly while another presents with microcephaly. The timing of the deviation from comparables and the specific brain structures which are affected are specific to each profile. The fourth profile appears to show no deviation from comparables. The results indicate that there is much that can and should change regarding autism treatment to ensure that each neurotype receives proper support.

Keywords: Autism; Neurodevelopment; Genetics; Subgroups

INTRODUCTION

Autism, also known as Autism Spectrum Disorder (ASD), henceforth to be referred to as Autism Spectrum Condition (ASC), is a neurodevelopmental condition that affects individuals in various ways. Common recognizable traits include difficulties with social interaction, communication and repetitive or restricted patterns of behavior, interests or activities [1]. ASC is considered a spectrum disorder because it affects individuals differently, with varying degrees of severity and a wide range of symptoms [2].

It's believed that such traits are caused by an atypical amount of sensory stimuli that is received and processed by the brain, leading to either hyposensitivity or hypersensitivity. Different senses may become more or less sensitive at different times. It's believed that hyposensitivity leads to more severe behaviors [3]. Sensory Processing Disorder (SPD) is not a separate diagnosis because it can coexist with other conditions. Not all who experience oddities with sensory processing and integration will exhibit communication difficulties. It's also believed by many in the medical community that traits presenting as SPD can be appropriate for young children [4].

Although ASC has been extensively studied, the causes are still unknown and it remains quite mysterious. Parents and caregivers often feel frustrated; the therapies and activities said to target troubling conduct seem rather straightforward, but the desired results never externalize. This isn't from a lack of trying. Early intervention services are common and most parents and pediatricians are well-versed regarding the signs and symptoms they should recognize in order for the child to receive assistance as early as possible. Most autistic children attend therapy; the time and effort involved can be intensive for the whole family. Applied Behavior Analysis (ABA) is an intervention therapy for autism. It purports to improve social interaction, improve or maintain positive behaviors and decrease troubling behaviors [5]. In 2017, it was estimated that the ABA market size was $17 billion. It's likely the market potential has grown by now. It's unfortunate that such a large market with no competition has

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been able to maintain the moniker of the gold-standard of autism therapy without much scrutiny or any studies which illustrate substantial improvement. Instead, it's been shown that ABA-based therapies lead to a reliance on specific prompts rather than cues [6]. Perhaps an inability to recognize social cues is a symptom of operant conditioning, the basis of ABA and not a trait of autism.

Several genetic mutations have been linked to neurological abnormalities that affect many on the spectrum [7]. However, this only accounts for a portion of individuals with ASC. It is still unclear what causes the atypical trajectory in most instances. Many cases of ASC are regressive-onset; learned behaviors are halted and autistic characteristics become apparent after infancy. The exact rate at which this occurs is unclear, although it's been shown that a loss of previously learned skills is observed in at least one-third of autism cases and possibly closer to 45% [8,9].

ASC does not appear to be a singular neurodevelopmental condition, but a collection of many. There is not just one brain-growth trajectory observed under the umbrella diagnosis of ASC but at least four [10-13]. Therefore, any assistance that may be truly helpful to one autistic neurotype may be less than ideal for the others. Without proper understanding of each profile, the condition could remain disabling. The unique trajectories observed among the autistic community largely involve the limbic system, which is the portion of the brain responsible for memory, sensory integration, emotional processing and movement, both conscious and unconscious [14]. ASC is diagnosed by only behavioral criteria; no physical, biological or neural markers are considered [15]. Because of the understanding of ASC as a spectrum condition, there are a multitude of ways in which behavior can be viewed which would lead to a diagnosis. The limbic system and basal ganglia are highly influential to both cognitive functions and automatic bodily processes. Since there are multiple ways that the growth of the limbic system varies among those diagnosed with ASC, there would be multiple reasons why behavior is affected.

LITERATURE REVIEW

Autism has become a household term, even among those who are not personally affected. Parents, teachers and pediatricians are aware of the outward signs that indicate a need for early intervention services. Despite this, ASC presents unique and pervasive challenges. This is in part due to the existence of various neurotypes. The stark differences between ASC profiles make it very difficult, if not impossible, to understand the condition entirely because the manner in which the brain perceives and responds to any sensory stimuli is markedly distinct. In order to create the proper environment and offer helpful support, the neurotype must be known. Behavior modification is unwise without understanding the unique profile and is unlikely to be required if consideration is given and acted upon regarding how that individual filters information from their environment. The founder of ABA stated that the process was only useful for auditory learners, not those who prefer visual stimuli. It's not uncommon for children to reach 8 or 9 years old before it is discovered that they need glasses, so toddlers and elementary-aged children should not take part in therapy which is dependent upon their ability to learn in one specific way.

By understanding how the neural anatomy differs, the behavioral profile of any patient takes on new meaning. The good news is this can largely be done without the use of brain imaging in children. Until the age of six, head circumference is a valid method of measuring cranial volume [16]. While this doesn't tell us which structures differ or how, the timing of the total brain-volume increase or stagnation is unique to each neural profile.

Challenges

In the 20 years between 1998 and 2018, the rate at which children were diagnosed with ASC increased 787% [17]. With the condition now understood to affect so many children, the field of autism research has grown exponentially. Information may have been hard to come by in previous decades, but much is currently being uncovered. This is a net positive, through any lens, but some findings can seem quite ambiguous or contradictory. This is to be expected, as the specific profiles have not yet been noted.

An area of interest among researchers in the field of autism is brain size. A large brain has long been associated with autistic characteristics, at least in childhood. Some studies have linked a larger brain with lower cognitive function and low Intelligence Quotient (IQ), but it may not be the best idea to label children in this way before they have a chance to grow into their neurotype. It's been observed that 35% of autistic children experience a dramatic increase in IQ by age 6 or 7. The tendency to use group means can hamper the understanding of important correlations by discounting outliers. Such practices make it difficult to decipher subgroups or misdiagnoses. For example, autism is typically associated with a large brain, for good reason. There certainly is ample evidence that proves large brains are more prevalent among the autistic community than the general population [18]. What hasn't been as apparent is that the smallest infant head circumferences are also found among those on the spectrum [19]. The use of group means in research serves to disguise this fact, since the percentage of large-brained infants is greater and their deviation from average is more substantial. In addition, there are not nearly enough longitudinal studies, which follow the same person throughout extended periods of time, capturing that particular individual's information over significant portions of life. This is the only way to reliably track divergent trajectories. Studying a group of autistic toddlers and comparing them with a different group of autistic adults won't yield substantial results. It's likely that by adulthood study participants would be fairly independent, as those needing more support may not be able to participate and the youngest group would have a mixture of those with high and low support needs.

Genetic conditions

It has been understood for decades that there is a strong genetic component to ASC. Studies performed on twins and siblings proved this fact long ago and it has been confirmed repeatedly. Identical twins are most likely to share an ASC diagnosis,

followed by fraternal twins and then siblings, who still have a higher likelihood to both have an ASC diagnosis than would be true among unrelated individuals. While there is no specific gene that causes autism, there are genes on every chromosome that have been implicated with the condition. So far, researchers have discovered well over 100 genes and counting that show some sort of connection. Not every autistic person has the same genetic mutation and there is no genetic mutation that causes autism every time it occurs. Many of these variations only manifest in the offspring and are not present in the sperm or egg.

Fragile X syndrome: Fragile X Syndrome (FXS) is characterized by intellectual impairment and behavioral issues, such as anxiety and hyperactivity. Autism is very closely linked to this condition; two-thirds of males with FXS match the criteria for ASC, while 1%-3% of those with an ASC diagnosis have FXS [20]. It is the leading cause of inherited intellectual impairment and affects far more males than females. Levels of impairment vary significantly. Some adolescents and adults are quite independent, while others need continual assistance [21]. Anxiety is common and about one-third of all males with FXS exhibit increased levels of aggression. Symptoms include cognitive challenges, delayed motor development and delayed speech.

Fragile X Mental Retardation Protein (FMRP) is produced by the *FMR1* gene. The expression of this RNA-binding protein is needed for proper synaptic plasticity and various neurological functions. FMRP is associated with gene expression and its absence can cause protein production to increase significantly in the brain, preventing the neuronal circuit from forming properly and impairing higher cognitive function [22]. Symptoms of FXS are less pronounced in females and not all females with the syndrome present with symptoms. This is because women have two X chromosomes, so if the *FMR1* gene on one of their chromosomes becomes damaged, their bodies can read from the other.

Rett syndrome: Rett syndrome is caused by another genetic mutation on the X chromosome, but females are predominantly affected in this case. The gene *MECP2* can mutate in multiple ways. Different mutations lead to more or less severe symptoms [23,24]. Growth and development are normal until sometime in infancy or near the first birthday. At this point, brain growth slows and there is regression in many areas.

Multiple brain functions are impaired, causing issues with movement, communication and even breathing. Some cases present with the presence of autoimmune antibodies in the brain that affect the development of at least two fetal brain proteins. These antibodies are passed to the fetus by the mother; rheumatoid arthritis and celiac disease are autoimmune disorders that are common causes. Twelve percent of mothers who have children with autism have such antibodies in their blood [25].

Four stages are observed such as stagnation, regression, pseudo-stationary and motor deterioration. The age of movement regression correlates with the age that height and/or weight regression occurs. The two do not happen simultaneously, but earlier loss of movement leads to earlier stagnation in body size. The following conditions are used to diagnose the disorder:

- Normal prenatal and perinatal history.
- Normal development until six months (or younger).
- Normal head circumference at birth.
- Slowed growth in head circumference after birth.
- Loss of voluntary hand movements between the ages of six months and two years.
- Stereotypical movement of hands.
- Language and social impairment.
- Regression and/or impairment of movement.

There is a concurrence with epilepsy in 80% of cases. Rett syndrome is very rare, affecting only about 1 in 10,000 females. However, it is the second most common reason for older women to experience neurological impairment, following Down syndrome [26].

Limbic system

The brain structures involved in the altered trajectories observed in ASC have wide reaching implications when it comes to expressed behavior. Situated between the cerebellum, which controls automatic bodily functions and the cortex, where analytical thinking takes place, the limbic system is highly connected to all areas of the brain and is able to send messages throughout. Structures in the limbic system are even able to freeze portions of the brain that are sending competing signals, so that the messages emanating from a specific limbic structure are felt more strongly. This is particularly true regarding the hypothalamus; each structure of the limbic system fights for its control. Some portions of the limbic system involve sensory input and processing, while other areas take that information to create the outward behavior that is observable by others. Each of the four ASC profiles differ in what structures are affected and how.

Amygdala: The amygdala is a small, almond-shaped structure in the temporal lobe, just above the ear, that is present in both brain hemispheres. Neurons in this area have multiple connections to other structures in the brain and it plays a key role in memory, behavior, decision-making and emotional responses. The amygdala is commonly referred to as the fear center and while that is a fairly good descriptor of the region, the amygdala is also involved with processing pleasure and rewards, as well as anger. Because of its importance in quickly processing complex emotions, the amygdala plays a role in many behaviors. The fight, flight or freeze response is controlled by this region; the body enters into survival mode before the logical mind is able to react to the situation. Because of its proximity to the prefrontal cortex, the area that controls logic, it can override rational responses, at least temporarily. On the other hand, logical thinking can eventually override an unfounded survival response from the amygdala. The amygdala and prefrontal cortex form the basis for emotional regulation and rational thinking in maturity. By adulthood, many multi-directional connections exist between these areas. These connections form over time and it is a slow process.

Hippocampus: This structure is essential for processing short-term memories into long-term memories. It holds the information for a time, then sorts and stores the data in the appropriate locations within the brain. Various types of brain cells execute specific functions during events. When researchers began studying this region of the brain, they were surprised to see that the data could be essentially read like a map. Place cells carry out one of the major functions of the hippocampus, spatial memory. These types of memories imprint information about the environment and one's place within it. Certain place cells are active only when the person is present in a specific location. Multiple place cells exist for the same area and which ones become active are dependent on the direction of movement [27]. The hippocampus is important in predicting what comes next and this is better understood by another type of cell present in the structure known as mismatch cells. When something unexpected is present or when something expected is moved, these mismatch cells begin firing. Activity in these cells is strongest when an outcome is similar, but not identical to what is expected. When mismatch cells are activated, lower performance on memory tests for old information is observed, while memory retrieval of new information is increased [28].

Hypothalamus: The hypothalamus produces various hormones, affecting behavior and involuntary functions. The location, abutting the brainstem, illustrates the control this area has over automatic bodily processes. The limbic system, the emotion and memory processing center of the brain, fights for control of the hypothalamus in various ways and has the ability to be the primary voice issuing commands regarding automatic bodily functions. The idea that emotions are all in the head with no physical significance couldn't be farther from the truth.

Basal ganglia: The basal ganglia are a cluster of nuclei that are found at the base of the brain and are the center of motor control. The entire area is immediately connected to the thalamus; all information must be sent through the thalamus before reaching any other part of the brain. Signals from the motor cortex travel through the basal ganglia as they make their way to the body. This is where all neural activity is consolidated into exhibited behavior.

Information flows through three distinct circuits which each have a regulatory effect on movement. The associative loop is active in training. Learning how best to perform specific movements is done through trial-and-error; cognitive planning is involved in each step. In the associative loop, the caudate nucleus receives information from all over the brain and projects to the thalamus. Eventually, the movement will become part of the motor loop. The motor loop becomes active with movements that are well-rehearsed. A routine has been constructed, which can be performed without conscious effort. Motor and sensory data is sent to the putamen which projects to the thalamus. The limbic loop coordinates facial expression, posture and gestures. Limbic information is routed through the caudate nucleus which projects to the thalamus and then back to the limbic system.

In each of these circuits, there are two pathways through which information travels; one serves to increase motor function while the other decreases motor function. Movements which are part of the goal are facilitated through the direct pathway and competing movements are inhibited by the indirect pathway. The balance is what reaches the thalamus and results in the end behavior [29].

Caudate nucleus: The caudate nucleus, along with the putamen, form the primary input into the basal ganglia. It is implicated in goal-directed activity, memory, flexible behavior and sleep. Motor responses to visual information are triggered here and it is important for learning with feedback. The caudate nucleus is required for displaying voluntary eye movement [30].

Substantia nigra: Dopamine is used by the substantia nigra to influence the basal ganglia. The release of dopamine is what brings about the good feelings from the achievement of a reward. Projections from the substantia nigra are sent to the putamen and caudate nucleus, which influence motor output [31].

Putamen: The putamen controls various cognitive functions, such as speech articulation, motor control, learning, rewards and addiction. Abnormalities of this structure have been linked to many conditions, including Parkinson disease, Alzheimer disease, Huntington disease, depression, obsessive compulsive disorder and ASC [32].

Globus pallidus: Implicated in both conscious and unconscious movements, the globus pallidus regulates the constant movement that's required for nearly everything, even speech. Signals are sent to the thalamus. Damage to this area results in tremors and jerky movements and imbalances are observed in Alzheimer disease and Huntington disease. It's also been shown that abnormalities within this structure are connected to the development of Obsessive Compulsive Disorder (OCD).

Four autism profiles

There is hesitancy among the autistic community to denote subgroups. Perhaps some may see it as an attempt to create a hierarchy, with one group better and the other group lesser. This is not likely to happen; a common personality trait among those of all profiles is a disregard for hierarchy. Even so, this level of self-imposed stagnancy is a phenomenon that doesn't seem to occur elsewhere in the field of mental health. It's imperative to understand all aspects of what is called autism. To do otherwise is to continue the cycle of ineffective therapy.

The existence of neurological profiles among individuals with ASC does not imply that specific profiles are low/high functioning or have low/high support needs. Such classifications exist among all profiles and may not be static when the individual is immersed in differing environments. It's imperative to provide individualized care to all individuals on the autism spectrum. The decades-long confusion regarding the umbrella diagnosis of ASC has created problems that wouldn't otherwise exist. Many have been put through what amounts to ineffective therapy because it was unnecessary. Behavior and speech modification, when not needed or initiated for the wrong reasons, can cause long-term harm.

Type A: A higher total brain volume is observed in toddlers and preschoolers with FXS. The excess growth is primarily located in

the caudate nucleus, which is a part of the basal ganglia. Interestingly, although the overall brain size is larger than comparables, the amygdala is smaller and less connected. The unique neural trajectory represents the first ASC profile, type A.

Brain size is increased early on, by six months of age, at the same time delays in achieving milestones are noted. Lack of expression, lack of gestures and difficulties with motor control are the telling signs that there is an issue. The volume of the caudate nucleus is significantly higher than that of both the ASC and comparable groups. As the size of the caudate nucleus increases, so does the likelihood of presenting with repetitive behaviors.

The caudate nucleus isn't the only basal ganglia structure that is enlarged. The globus pallidus and putamen are also increased in size in comparison to the ASC and comparable groups by six months of age. The neurological and behavioral abnormalities occur in rapid succession, leading to a condition that is easily diagnosable at young ages [33].

This neurotype is observed in all patients with FXS, not just among those who have been diagnosed with ASC. The enlarged neural structures are present early in infancy, by six months of age and a simple head circumference measurement will indicate that the cranial volume has increased.

Type B: A large head has always been associated with autism. Upon close inspection, this makes sense, as there are two profiles that each present with megalencephaly. This, along with the use of group means, has served to hide autism type B. The use of group means in research is standard practice, as it can aid in the comparison of multiple groups. However, in this case it has served to hide a group, likely preventing those in need from receiving the proper help and support.

The autism type B neural trajectory is that which is observed in Rett syndrome. There is an interruption in brain development early in infancy, by six months old. The brain does not regress in size; it simply remains small. There are similarities with Parkinson disease that go far beyond a loss of fine motor control. There is less melanin in the pars compacta of the substantia nigra, which colors dopamine-producing neurons. Therefore, less dopamine is released into the caudate nucleus and putamen, which inhibits decision-making, executive function, reward and consequence.

Irregularities are observed in the cortex, limbic system, autonomic nervous system and peripheral nervous system. Gliosis commonly occurs on the spinal cord and cerebellum. Gliosis is akin to scar tissue for the central nervous system. It fills an area where there was an injury, although in this case there is no apparent cause for the damage.

Type C: Autism type C is the second neurotype presenting with megalencephaly. The specific areas of the brain that are larger, the amygdala and the hippocampus, are integral components of memory formation and recall. Amygdala overgrowth begins between the ages of six months and one year; social deficits become noticeable about a year later. An increase in the size of the amygdala correlates more strongly with an increase in social difficulties than it does with repetitive behaviors, although most traits take time to fully form. This makes diagnosis difficult at young ages.

It's not just the size of the amygdala that is increased. Postmortem studies show that the amygdala in children with ASC is densely packed with neurons, which in turn have denser dendrites or signal receptors. Enlargement of the visual cortex is observed in conjunction with the increase in amygdala size.

Type D: Surprisingly, there are many children on the spectrum who do not present with any neural abnormalities at all. The growth of their brains and the structures within do not deviate from comparables at all. There are clearly genetic and neural components to the cause(s) of ASC and the existence of a typically developing trajectory opens the possibility of another source. Possibly there are environmental or social factors involved.

It's possible that the rush to diagnose autistic children in order to begin early intervention therapy during crucial years of language development has created language and social difficulties that would not have otherwise existed. Prompt dependency, a well-known effect of autism therapy, has been shown to prevent the development of social skills and interpersonal relationships in children [34].

DISCUSSION

The timing of the changes in head circumference is a key factor in differentiating between neurotypes and this can be easily accomplished by keeping records of the measurements throughout infancy and the toddler years. Type A is observed with a cranial circumference that rapidly expands at around six months old. It's possible for there to be some regression, but generally a lack of meeting further milestones is noted. Also at around six months old, type B presents with a head that stops growing at all. Possible regression and an end to meeting proper milestones begins immediately at this time. The second neurotype presenting with megalencephaly, type C, exhibits an increase in cranial volume occurs at a later time than what is observed in type A. This occurs between 6-12 months, sometimes later. Regression isn't always noted right away, as is true for the other two types. Sometimes changes aren't exhibited for up to a year [35]. Type D has a neural trajectory that does not deviate from controls at all, adding a layer of confusion and difficulty in determining what supports are appropriate.

CONCLUSION

The treatment of ASC has shown pervasive challenges, which are apparent in the lack of positive results experienced by those who have undergone therapy for the condition. The existence of multiple and distinct neurotypes which are disregarded in both the diagnostic and treatment stages makes it impossible to curate appropriate therapy for young children. Because behavior modification is harmful when initiated unnecessarily or in the wrong manner, current early intervention services must undergo a radical and immediate transformation, which takes the individual neurotype into consideration. Upon reviewing the multiple trajectories, it's clear that there is a myriad of causes for the condition, some of which are yet to be uncovered.

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