Review

Neurobehavioral perspectives on autistic spectrum disorder

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DOI: https://doi.org/10.56280/1628860368

Received 9 April 2024 Accepted 10 May 2024 Online published 18 May 2024

Abstract

Understanding genetics and environmental influences in autism has been explored in greater depth in recent decades. However, the mechanism by which they converge that leads to autism still needs to be explored further. An autism diagnosis in DSM-5 results from a neurodevelopmental disorder hurting normal brain function, affecting communication and social interaction combined with restricted or repetitive patterns of behavior and interests. This paper reviews current work investigating how the underlying mechanism of the brain structure and function relates to the complex and aberrant behavioral manifestations of autism. Mapping this connection can provide us with a better understanding of autism signs and symptoms, making the process of accurate diagnosis more straightforward. As a complex neurobehavioral condition, autistic individuals process the environment and their interactions with others differently from those without autism. So, they make different perceptions and connections between themselves and the environment. Consequently, they will have difficulty communicating, forming relationships, and responding appropriately to their environment. It is this lifelong neurobehavioral dysfunction that prevents autistic individuals from adequately understanding what they perceive and the emotional expression of others. There will be differences in their mental states, how their brains work, and how their thinking processes will be affected by a neurodevelopmental disability.

Keywords: Autism spectrum disorder (ASD), brain growth, development, cognitive shifting, impaired communication, social behavior, prefrontal cortex, amygdala, neuroanatomy, neurobehavioral disorder, neurobiological mechanisms.

1. Introduction

The neurobehavioral underpinnings of autism seek to identify what cognitive deficits are present and their implications for behavior, emotion, and learning. Autism is a condition related to brain development caused by a variety of biological factors that result in a single individual cognitive deficit, which eventually results in a variety of behavioral signs and symptoms. The disorder is complex and impacts how an autistic individual perceives and socializes with others, causing significant communication and social interaction challenges combined with rigid and repetitive patterns of behavior. Because of the wide range of symptoms and severity, this condition is now called autism spectrum disorder (ASD).

Affected individuals can also have a wide range of intellectual disabilities and social-communicative impairments. Most people with ASD have mild to moderate intellectual disability, while others have average to above-average intelligence. Some have cognitive abilities that greatly surpass their overall level of functioning, often in areas such as music, mathematics, or memory.

However, in milder cases, the disorder is identified at a later age. Approximately one third of children exhibit intellectual disability. Prior to ASD, conditions that were previously considered separate were included - autism, Asperger's syndrome, childhood disintegrative disorder and an unspecified form of pervasive developmental disorder[1]. In some circle autism is still used to refer "Asperger's syndrome," which is generally thought to be at the high functioning or to be on the mild end of ASD.

In most cases, children with autism typically exhibit developmental disorders during the first three years of life, and affects the brain's normal development of social and communication skills and repetitive sensory-motor behaviors (Khan et al., 2012; Shen, 2017). The severity of a condition can sometimes be difficult to determine since each child has a unique mixture of symptoms. It's generally based on the level of impairments and how they impact the ability to function.

[1] American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. Washington DC: American Psychiatric Association; 2013.

Journal of Multiscale Neuroscience

Autism is believed to be a condition that can be attributed to a variety of biological causes, which all result in one individual cognitive deficit, which in turn results in a variety of behavioral presentations, as shown in **Figure 1**. Despite an organic etiology for autism, the consequences are not well understood about what causes the neurological differences and how these differences manifest themselves. The etiology of autism is complex and multifaceted, likely resulting from genetic, neurological, and environmental factors. It has been suggested that some combination of 1) Genetic predispositions and 2) Gene by environmental interactions 3) Result in brain abnormalities, which in turn are the causes of the range of behaviors we currently refer to as autism spectrum behaviors. ASD results from a combination of risk-associated genes, de novo mutations, and environmental factors resulting in molecular, neurological, and behavioral changes (Gadad et al., 2013; Geschwind, 2008). Individuals with ASD often show a decreased preference for social stimuli compared to neurotypical individuals. Research implicates particular brain regions in social decision processes, including the prefrontal cortex, amygdala, the sub-region of the hypothalamus, hippocampal temporoparietal and limbic structures (Gangopadhyay et al., 2021; Seo & Lee, 2012; Bault et al., 2011). Circuit-level research using animal models, such as rodent and primate, social preference behaviors has largely supported the involvement of the neural circuits encompassing the prefrontal cortex and the amygdala (Haber & Knutson, 2010; Dal Monte et al., 2020; Gangopadhyay et al., 2021). Understanding how these specific prefrontal-subcortical circuits contribute to social preference behaviors could assist applied clinical research on ASD.

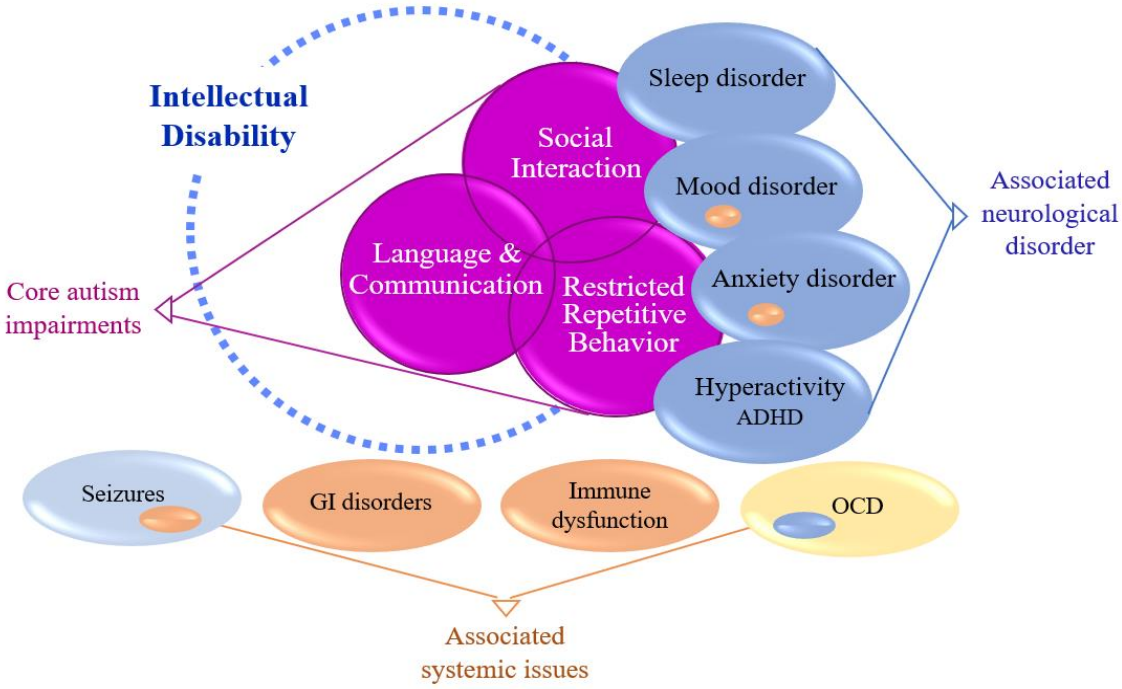

Figure 1: Illustrates common outcome how autistic individuals often have deficits in social interaction; language and communication and have restricted or stereotyped patterns of behavior. It is also possible for autistic individuals to have co-morbid neurological disorders that include intellectual disability, seizures, mood, and anxiety disorders. These disorders typically manifest in the early stages of development. Delays in adaptive functioning is common across many neurodevelopmental disorders, particularly ASD. The severity of each will vary between individuals over time. Core autism impairments of ASD likely affect the child's social-emotional development, language development and cognitive development. Furthermore, these aspects of development are interconnected.

Alongside autism, several medical conditions can appear at any time during a child's development, such as epilepsy, depression, anxiety, and attention deficit hyperactivity disorder (ADHD), as well as challenging behaviors like low/ cranky mood, poor sleep and appetite, irritability, and a loss of motivation. (Summers et al., 2017; Al-Beltagi, 2021). The level of intellectual functioning among autistic people varies widely, extending from profound impairment to superior levels.

The unique combination of symptoms that autistics exhibit can sometimes make it challenging to assess their severity. Those with mild intellectual disability are slower in all areas of conceptual development, significantly reducing their capacity to engage in social activities and interests (Vivanti et al., 2013; Dykens & Lense, 2011). Hence, an individual's ability to function will generally be determined by the impairment level and how it impacts their capacity. Likely that several functional neural loops are implicated, and all impinge on neurocognitive/social cognitive functions that are crucially impaired in autism (Gillberg & Coleman, 2003). Various genetic or medical conditions can sometimes be associated with the ASD syndrome, which is characterized by a high rate of mental retardation and seizure disorder (McBesag, 2017).

Currently, research indicates that a single factor does not cause autism spectrum disorder and is likely caused by a wide range of factors based on its diverse symptoms and severity. These causes range from genetic to environmental factors to neurological abnormalities (Ford et al., 2023; Hirota & King, 2023). There is evidence that these factors may increase the likelihood of a child developing ASD. Taken together, there has been an incredible amount of effort put into determining the etiology and risk factors of autism since it was first identified as a diagnosis (DSM-5). There are a wide variety of causes that can contribute to autism, such as genetic factors, environmental factors, and neurological abnormalities (Kanner, 1943; Cook et al., 1997; Bolton et al., 2001).

2. Genetic causes of autism

Several studies have linked the genetic component of ASD. According to every twin study focusing on autism spectrum disorders, monozygotic twins are more likely to co-occur with ASD (Lichtenstein et al., 2010; Ronald & Hoekstra, 2011). This cause of ASD is also confirmed in another study by Warren and his colleagues, who discovered that relatives of individuals with ASD have a significantly higher risk of also having the disease than the general population (Warren et al., 2012, Posthuma & Polderman, 2013). Genetic factors, abnormal brain development, abnormal neurochemistry, and abnormal brain function are the main causes of autism (Lenroot & Giedd, 2008).

There is no question that genetic factors – rare mutations, deletions, and copy number variants, contribute to the development of autism (Geschwind, 2011). There is genetic evidence for ASD in every twin study that has focused on the disorder, which found that monozygotic twins have a higher likelihood of co-occurring with the disorder (Tick et al., 2016; Bailey et al., 1995). Monozygotic twins, who share the same genetic makeup, have consistently shown higher concordance rates for ASD compared to dizygotic twins (Geschwind, 2011). It has been demonstrated that autism is highly heritable through the research of several teams. When one identical twin has autism, it is about 80 percent likely to have autism that the other identical twin has it too (Chaste & Leboyer, 2012).

Several different genes appear to be involved in autism spectrum disorder. For some children, autism spectrum disorder can be associated with a genetic disorder, such as Rett syndrome or fragile X syndrome. For other children, genetic changes (mutations) may increase the risk of autism spectrum disorder (Hodges & Fealko, 2020). Still, other genes may affect brain development or how brain cells communicate, or they may determine the severity of symptoms (Miller & Whelan, 2010). Some genetic mutations seem to be inherited, while others occur spontaneously. However, genetics is not entirely responsible for a child's chances of having autism, and environmental factors also contribute to the condition.

3. Environmental causation of ASD

Long standing research links environmental factors can influence the manifestation of symptoms during early childhood development and throughout life. When the child is still in the womb, factors such as mother stress and nutrition can impact the child's developing brain and body (McEwen, 2011). These environmental factors can affect growth patterns, behavior, and health changes. During formative years of a child's life, stress and nutrition can significantly impact the development of the child's brain. Currently, researchers are investigating whether factors such as viral infections, medications, complications during pregnancy, and chemical or air pollutants play a role in triggering

autism spectrum disorder (Ohkawara et al., 2015). Some environmental influences, such as exposure to a maternal immune response in the womb, the mother's nutrition or complications during childbirth, may contribute to the development of autism or intensify its symptoms (Beversdorf et al., 2019).

Evidence suggests that an environmental factor could contribute to autism's development, as indicated by two major sources of causality: (1) the Current understanding that human brains are particularly vulnerable to environmental toxicants during development (Dufour-Rainfray et al., 2011) and (2) generally important, an assessment of the connection between autism and environmental exposure during prenatal development (Landrigan, 2010; King, 2011). At this stage, the brain is very vulnerable to destruction, and the disruption of connections may result in serious neurological consequences. Thus, environmental risk factors for autism must be identified so that experts can find a way to reduce their risks. However, the factors backed by the strongest evidence are not easily modifiable (Grabrucker, 2012). Nevertheless, more research needs to be done into environmental factors that play a role in autism because of the unabated rise in childhood ASD.

Considering the impairment of neurobehavioral abnormalities due to ASD, it may be reasonable to postulate a hub region within the brain that links social behaviors and repetitive behaviors (**Figure 2**). Considering this perspective, the amygdala plays a crucial role in the perception of emotions such as anger, fear, and sadness, as well as controlling aggression. There is perhaps no single neurobiological marker for ASD more widely accepted than abnormal amygdala function (Pelphrey et al., 2011; Kleinhans et al., 2010). It has been consistently linked that amygdala dysfunction is associated with deficits in social intelligence, motivation, and perception, particularly among individuals with ASD (Chevallier et al., 2012; Pelphrey et al., 2011).

4. Parts of the brain affected by ASD

Neuroimaging studies have provided considerable insights into the underlying neurobiological mechanisms of ASD. Existing autism research has re-

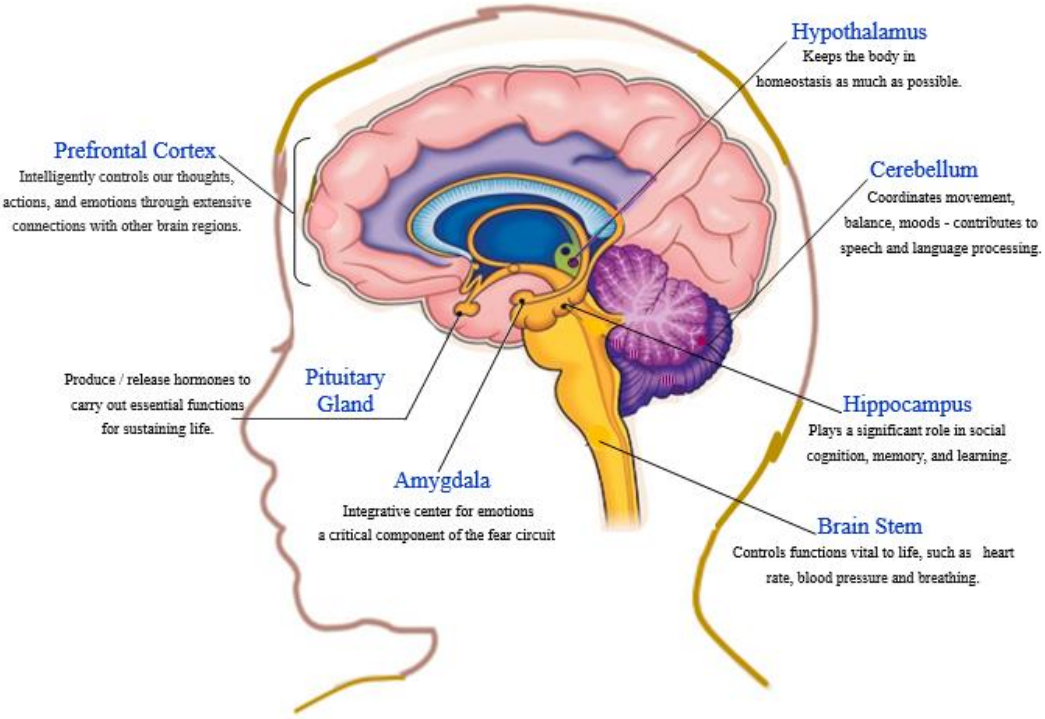

Figure 2: Depicts a condensed view of some brain regions that are known to be structurally different in individuals with autism. To understand what part of the brain is affected by autism, it's important to understand the role of certain key brain structures. Anatomy of the inside of the brain showing the amygdala, prefrontal cortex, hypothalamus, pituitary gland, cerebellum and the brainstem, and other parts which have been suggested to mediate clinical phenotypes of ASD. They comprise the putative neural systems implicated in the functions that are most impacted by the core features of autism.

vealed that certain brain regions are structurally different in individuals with autism using magnetic resonance imaging (Hazlett et al., 2005). The nature of what differentiates neurotypical individuals from those with autism has been better understood through research. It has been discovered that the autistic brains differ in several ways. These include differences in overall brain size and the structure and function of certain brain regions.

There tends to be some irregularities in the brain structures of some children with autism as condensed in **Figure 2**. The most striking observation is that brain structure abnormalities or malformations can trigger symptoms of autism (Li et al., 2023). Detailed examination and structured magnetic resonance imaging studies reveal abnormalities in the frontal lobes, amygdala, hippocampus and cerebellum as pathological in autism (Ecker et al., 2015; Brun et al., 2009). Another comparable investigation provides insights into the neural substrates and autistic symptoms across the human life cycle and their implications of neurodevelopmental characteristics underlying ASD (Ecker et al., 2015; Maximo et al., 2014). There are many ways in which the components of the neural systems in ASD that are linked to producing clinical symptoms have been investigated.

Prefrontal cortex dysfunction is extensively implicated in autism to explain deficits in cognitive, linguistic, social, and emotional functions (Morrison et al., 2020). Studies have pointed out that people with autism tend to have a thicker cortex than people without autism (Khundrakpam et al., 2017). Persistently growing brains indicate aberrant development or inability to prune connections within the cortex (Herbert, 2005; Minshew et al., 2007). It may be because of this difference that people with autism often have difficulty with social interaction and communication.

A foregoing study by Van der Heijden et al. (2021) recognized that people with autism often have cerebellum size, shape, and function abnormalities. These abnormalities can lead to problems with motor skills, balance, and coordination and difficulties with cognition, social interaction, and communication (Pierce & Courchesne, 2001; Ohalloran et al., 2012). Without subtlety, a clear distinction can be seen between people with autism and those without autism in terms of how the cerebellum is structured and functions. In another work of similar nature, autistic people showed less activity in the cerebellum during a task that required them to plan and execute movements (Amaral et al., 2008; Brun et al., 2009). It can be seen, therefore, that these differences in the cerebellum play a role in the development of the condition and its associated difficulties in autism.

The hippocampus, another vital brain structure crucial for memory formation, navigation, and cognition, may also be implicated in autism. According to research, autistic individuals have larger hippocampi and different shapes from neurotypical individuals. (Banker et al., 2021). As it has been acknowledged, alterations in the hippocampus can lead to memory impairments and difficulties in learning new information or recalling past experiences (Willimas et al., 2006).

Well-documented reports indicate that autistics have distinct patterns of brain development. Detailed examination of some children revealed more volume in their amygdala, where overgrowth begins before 3 years of age, about the time impairment becomes clinically evident (Schumann et al., 2004; Courchesne et al., 2001). The enlarged amygdala becomes hypersensitive to possible threats and triggers false alarms (Kerns & Kendall, 2012; Cacha & Poznanski, 2022). This may explain why autistic individuals avoid social situations or become overly upset when routines are altered. It should be noted, however, that as autistic individuals age, the structural volume of their amygdala decreases (van Steensel et al., 2012; Courchesne et al., 2011; Dziobek, 2006). Changes in the amygdala in individuals with autism may contribute to difficulties in emotional regulation and social interaction. Autism significantly impacts the amygdala, which mediates many aspects of emotion, motivation, and adaptive social behavior (Adolphs, 2008).

Pertinent empirical observation found that children with ASD are more likely to suffer from dysfunctions in the HPA axis (Gao et al., 2022). It is apparent that the hypothalamic pituitary adrenal (HPA) axis has a long history in studying neurocognitive aspects of diseases such as autism and other mental health problems (Spratt et al., 2012; Cacha et al., 2020). Supplementary to this study is the inquiry into morphological changes in the hypothalamus are anatomically correlated with the defining characteristic of autism (Caria et al., 2020). Several structural and functional changes occur in the brainstem via the amygdala, cerebellum, thalamus, and basal ganglia that contribute to the symptoms of ASD (Amaral et al., 2008; Kleinhans et al., 2010; Herrington, 2016). What is essentially involved is the stress response by HPA hormones, such as cortisol, glucocorticoid, and

adrenaline, that can be observed in the adrenal glands (Cacha & Poznanski, 2022; Handa & Weiser, 2014).

Together, these differences/responses in the brain and underlying brain changes leading to altered structural connections and functional coordination within the brain network explain autistic behaviors similarly (Leisman et al., 2018). These differences contribute to the unique cognitive and behavioral characteristics observed in individuals with ASD.

5. Conclusion

ASD is a complex neurodevelopmental condition clinically characterized by some degree of difficulty with social interaction and communication, as well as repetitive patterns of behaviors. Typically, the signs and symptoms of autism become evident in children during the first three years. In addition to challenging behaviors, ASD is frequently associated with common neurological comorbidities such as epilepsy, depression, anxiety, sleep disturbances, temperament, and attention deficit hyperactivity disorder. There is also a strong element of intellectual disability in children with ASD. Although the level of intellectual functioning among autistics varies significantly, ranging from profound impairment to superior capabilities depending on their level of development.

While the paper has some limitations, it supports the idea that abnormal brain structures in certain region's volume, size, thickness, and overall head size are associated with ASD. When it comes to abnormal brain development, genetic influences play a major role in the genesis of ASD. However, environmental factors alone may explain some cases, and they are also thought to increase autism risk by interacting with genetic susceptibility. In future research, understanding how genetic and environmental risk factors converge might serve as a valuable starting point for future work toward uncovering the physiological processes associated with autism.

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