The Relationship Between Abnormal Cerebellar Development and Autism Spectrum Disorder: A Postprint

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Abstract

Abstract Although the cerebellum constitutes only 10% of the total human brain volume, it contains more than half of all neurons. Previously considered to primarily control limb motor coordination, accumulating evidence in recent years has demonstrated that the cerebellum is intimately involved in higher cognitive functions such as learning, attention, and language, participating in the regulation of diverse non-motor functions. Concurrently, abnormal cerebellar development is closely associated with numerous neurodevelopmental disorders, including Autism Spectrum Disorder (ASD), also known as autism, a typical neurodevelopmental disorder characterized by social deficits, repetitive stereotyped behaviors, and language impairments, often accompanied by sensory abnormalities. Clinical studies have revealed that ASD patients commonly exhibit alterations in cerebellar structure and function. Intriguingly, similar abnormal cerebellar phenotypes have been observed in ASD animal models. Importantly, specific knockout of ASD susceptibility genes in cerebellar neurons can induce autism-like behaviors in animal models, suggesting that abnormal cerebellar development represents one of the key pathological mechanisms underlying ASD. This review will briefly summarize the relationship between the cerebellum and ASD from both clinical and basic research perspectives, offering new insights for the diagnosis and treatment of ASD.

Full Text

The Relationship Between Abnormal Cerebellar Development and Autism Spectrum Disorder

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Abstract

Although the cerebellum comprises only 10% of total brain volume, it contains over half of all neurons in the human brain. Traditionally regarded as primarily controlling motor coordination of limbs, accumulating evidence in recent years has demonstrated that the cerebellum is intimately involved in higher cognitive functions such as learning, attention, and language, participating in the regulation of various non-motor functions. Concurrently, abnormal cerebellar development is closely associated with multiple neurodevelopmental disorders, including Autism Spectrum Disorder (ASD). ASD, also known as autism, is a typical neurodevelopmental disorder characterized by social impairments, repetitive stereotyped behaviors, and language deficits, often accompanied by sensory abnormalities. Clinical studies have revealed that individuals with ASD typically exhibit structural and functional alterations in the cerebellum. Interestingly, similar cerebellar abnormal phenotypes have been observed in ASD animal models. Importantly, specific knockout of ASD susceptibility genes in cerebellar neurons can induce typical autism-like behaviors in model animals, suggesting that abnormal cerebellar development represents one of the key pathological mechanisms underlying ASD. This review briefly summarizes the relationship between the cerebellum and ASD from both clinical and basic research perspectives, providing new insights for the diagnosis and treatment of ASD.

Keywords: autism, cerebellum, structure and function, model animals

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by core clinical features including social impairments, repetitive stereotyped behaviors, language deficits, and sensory abnormalities (Hirota & King, 2023). Globally, the incidence of ASD has been increasing annually, affecting over 1% of the population worldwide (Bouzy et al., 2023). Researchers generally agree that the prevalence of ASD is higher in males than in females during childhood (Alaerts et al., 2016; Hu et al., 2022). The exact causes of ASD remain incompletely understood, though studies indicate that both genetic and environmental factors play critical roles in its development (Cheroni et al., 2020). Nevertheless, clinically effective diagnostic and therapeutic strategies remain insufficient, imposing tremendous burdens on patients' families and society. Therefore, in-depth investigation of the pathological mechanisms of ASD holds significant clinical and practical importance.

Traditionally, the cerebellum has been primarily regarded as a central nervous

system structure coordinating voluntary movement, gait, and posture (Carey, 2024). However, mounting research evidence demonstrates that the cerebellum also participates in regulating multiple higher cognitive functions, including cognition, attention, memory, language communication, emotional regulation, and executive function (Prati et al., 2024). Consequently, some researchers propose that the cerebellum may be one of the pathological brain regions closely associated with the occurrence and development of ASD (Stoodley et al., 2017). Preliminary clinical and animal model studies have shown that both ASD patients and mouse models exhibit difficulties in motor coordination and learning, further supporting the role of the cerebellum in ASD pathology (Wu & Zhang, 2016). This article briefly reviews research progress on abnormal cerebellar development and ASD and outlines future research directions.

2. Basic Structure of the Cerebellum and Its Connections with the Cerebrum

The cerebellum is located posterior to the brainstem and consists of two symmetric hemispheres. It is primarily composed of gray matter on the surface and white matter internally. The cerebellar nuclei are situated in the central region of cerebellar gray matter, including the fastigial nucleus, globose nucleus, emboliform nucleus, and dentate nucleus. The cerebellar cortex is divided into three layers: the molecular layer (ML), Purkinje cell layer (PCL), and granule cell layer (GCL). The cortex contains various types of neurons, including stellate cells (SC), basket cells (BC), Purkinje cells (PC), Golgi cells (GoC), and granule cells (GrC) (Farini et al., 2021). The main input pathways are mossy fibers (MF) and climbing fibers (CF). The axons of granule cells extend upward to the molecular layer, where they bifurcate in a T-shape and run in opposite directions along the longitudinal axis of the folia, forming parallel fibers (PF) (Pijpers et al., 2006). During cerebellar cortex development, the proliferation rate of granule cells in specific regions accelerates, pulling inward along the axons of Purkinje neurons and creating inward depressions in the cerebellar cortex at these sites. As the cerebellar cortex develops outward, the characteristic foliated structure of the cerebellum gradually forms.

The cerebellum connects with the cerebrum through multiple neural pathways, including cerebello-brainstem pathways, fiber tracts connecting cerebellar nuclei with the cerebral cortex, and bidirectional pathways through which the cerebellum transmits information to the cerebral cortex via the brainstem and receives return signals (Sokolov et al., 2014). These connections are crucial not only for motor control but also for the regulation of cognitive, emotional, and other higher neural functions, making the cerebellum a key component for the efficient operation of the entire nervous system (Wang et al., 2020). The brains of individuals with ASD show atypical functional connectivity patterns, particularly reduced long-distance connections and enhanced local connections (Zhang et al., 2015). Simultaneously, connectivity between the cerebrum and cerebellum also appears abnormal.

3. Cerebellar Abnormalities and Motor Impairments in Individuals with ASD

Cerebellar structural abnormalities in individuals with ASD typically involve abnormal cerebellar volume, vermal hypoplasia, and reduced Purkinje cell numbers along with changes in neuronal size (Courchesne et al., 2004). Although cerebellar volume is generally considered smaller in individuals with ASD, Piven and colleagues found enlarged cerebellar volume in some ASD individuals, indicating that cerebellar volume abnormalities in ASD are not universally characterized by selective reduction (Piven et al., 1997). Magnetic resonance imaging (MRI) has been widely used since the 1980s to analyze brain structure in individuals with ASD. MRI images from ASD individuals show that multiple cerebellar regions, particularly lobules VI and VII, are generally smaller in area. This reduction in cerebellar regions is typically considered a result of congenital hypoplasia rather than postnatal atrophy or deterioration. Consequently, this localized developmental abnormality can serve as a temporal marker to identify specific events or processes affecting brain development in ASD (Courchesne et al., 1988; Hodgdon et al., 2024). In individuals with ASD, cerebellar structural abnormalities may directly affect motor and cognitive functions because important connections exist between the cerebellum and brainstem, hypothalamus, and thalamus, and abnormalities in these connections may indirectly affect the normal development of cerebello-cerebral circuit systems involved in motor, cognitive, and sensory functions (Strick et al., 2009). Abnormal cerebello-cerebral functional connectivity plays a significant role in core ASD symptoms such as social and communication impairments and repetitive stereotyped behaviors, suggesting that abnormal cerebello-cerebral functional connectivity may be one of the potential neural mechanisms underlying cognitive and sensory impairments in ASD (Zhang et al., 2022). Cerebellar abnormalities may disrupt the structural and functional optimization of specific cerebello-cerebral circuits in individuals with ASD. In ASD patients, abnormal connectivity between the cerebellum and cerebrum manifests as either hypoconnectivity or hyperconnectivity, which may limit information transmission or cause processing disruptions, thereby affecting cognitive, social, and perceptual functions (van der Heijden et al., 2021). Specifically, connectivity strength between the cerebellum and sensorimotor cortex is increased, while connectivity with cerebral cortical regions related to cognitive functions is decreased (Noonan et al., 2009; Khan et al., 2015). Such abnormal connectivity typically results from cerebellar developmental disorders and may contribute to neurodevelopmental impairments in ASD.

One of the primary characteristics of ASD is repetitive stereotyped behaviors, such as hand flapping, foot stomping, tongue licking, and object spinning. Similar to ASD, individuals with cerebellar vermal agenesis, reduced cerebellar volume, and cerebellar hypoplasia also frequently exhibit comparable repetitive stereotyped behaviors (Hampson & Blatt, 2015). Individuals with cerebellar lesions typically show motor coordination deficits such as ataxia and dysmetria (Flament & Hore, 1986). Similar motor coordination impairments have

been observed in individuals with ASD. Motor impairments in ASD manifest as delays and deficits in motor development, including delays in gross and fine motor skills, as well as deficits in motor learning, balance coordination, and gait (Thomas et al., 2022). Up to 80% of children with ASD display motor coordination impairments, which are highly correlated with ASD severity and IQ levels (Rudolph et al., 2023). Research indicates that children with ASD often struggle with skilled movements, which may be related to demands for basic motor skills, knowledge of motor representations, and the translation of these representations into motor plans. These phenomena suggest that mental impairments in individuals with ASD may be associated with impaired formation of spatial representations, transcoding of representations, and execution, potentially related to abnormal distribution and connectivity across parietal, premotor, and motor circuits (Dowell et al., 2009). These motor impairments in ASD may be directly or indirectly related to cerebellar abnormalities, although the underlying mechanisms remain incompletely understood.

4. ASD-Like Symptoms in Individuals with Cerebellar Lesions

Schmahmann and colleagues proposed that cerebellar damage may lead to cerebellar cognitive affective syndrome (CCAS), characterized by deficits in executive function, language processing, spatial cognition, and emotional regulation—features that overlap with core symptoms of ASD (Schmahmann & Sherman, 1998; Casartelli et al., 2018). Cerebellar abnormalities such as congenital cerebellar malformations, cerebellar tumors, Joubert's syndrome, cerebellar developmental delay, and cerebellar atrophy increase the risk of neurodevelopmental disorders in children and may lead to ASD-like behavioral manifestations (Bolduc et al., 2012). Among children with congenital cerebellar malformations, neurodevelopmental delays and ASD are prevalent. Statistical analysis of a certain sample size of patients with congenital cerebellar malformations revealed an ASD incidence rate of 12% in this population (Pinchefsky et al., 2019). Additionally, approximately 25% of children with Joubert's syndrome are diagnosed with ASD, with cerebellar vermal hypoplasia being a prominent feature (Geschwind & Levitt, 2007). Cerebellar fiber damage in children with posterior fossa syndrome is also closely associated with increased incidence of ASD-like behaviors (Catsman-Berrevoets & Aarsen, 2010). Cerebellar atrophy is the most common neurological abnormality in individuals with ASD, and early cerebellar atrophy is closely associated with increased ASD incidence and risk, particularly prevalent in premature infants. As medical technology advances and survival rates of premature infants improve annually, the risk of developing ASD further increases (Rout & Dhossche, 2008). Therefore, in-depth investigation of the association between abnormal cerebellar development and ASD is particularly important.

5. Mouse Models of Abnormal Cerebellar Development and ASD

Although clinical imaging studies suggest a close correlation between abnormal cerebellar development and ASD, current research still lacks direct causal evidence. Utilizing model organisms allows for more direct exploration of causal relationships and preliminary analysis of mechanisms at the genetic, molecular, and cellular circuit levels. Indeed, various abnormalities have been observed in the cerebellum of rodent ASD models, including altered cerebellar morphology, increased foliation number (Yang et al., 2015), Purkinje cell loss (Sudarov & Joyner, 2007), abnormal proliferation of granule neurons (Wefers et al., 2017), and synaptic connection abnormalities (Lai et al., 2021). Furthermore, specifically affecting cerebellar neural development in mice can lead to ASD-like phenotypes, suggesting that abnormal cerebellar development may be one of the key factors triggering ASD.

5.1 Morphological and Functional Alterations in Mouse ASD Models

Valproic acid (VPA) is a drug widely used to treat epilepsy and seizures, with good tolerance and high safety in adults. However, studies have shown that VPA has strong teratogenic effects, potentially causing mild neurodevelopmental disorders or even congenital malformations (Chen & Xu et al., 2024). Particularly, prenatal VPA exposure has been found to increase the risk of ASD in children (Gholipour et al., 2024). Therefore, prenatal VPA exposure has become a common non-transgenic ASD animal model, widely applied in zebrafish and rodents. Studies in rats have shown that after VPA exposure, the number of Purkinje cells in the cerebellar vermis and hemispheres is significantly reduced, while some studies have found reduced nuclear area, shortened nuclear length, and increased nuclear cell numbers in deep cerebellar nuclei of VPA-exposed rats (Wang et al., 2018). Additionally, VPA exposure leads to changes in microglial density in the rat cerebellum. Microglia, as immune cells in the brain, typically respond to injury and pathological development (Gifford et al., 2022).

Maternal immune activation (MIA) animal models are increasingly used to study immune-mediated neurodevelopmental disorders such as ASD. Recent research has shown an association between maternal infection during pregnancy and ASD onset in offspring (Tartaglione et al., 2022). Experimental administration of Poly(I) to pregnant mice to simulate maternal immune activation resulted in offspring exhibiting ASD-like behaviors including reduced social behavior and increased repetitive stereotyped behaviors. Further studies revealed that Poly(I) treatment of pregnant mice caused Purkinje cell loss and delayed granule cell migration in offspring mice, producing lasting effects on cerebellar morphology and various motor and non-motor behaviors (Shi et al., 2009). Overall, these studies indicate that MIA is a risk factor for ASD, though the specific association with the cerebellum requires further in-depth exploration and research.

Additionally, some conserved ASD susceptibility genes also significantly affect cerebellar development in mice. For example, the CNTNAP2 gene is widely expressed in cerebellar Purkinje cells, regulating their morphology, and its mutation can cause cerebellar malformations and mild cerebellar ataxia behavioral deficits in mice (Fernandez et al., 2021). Moreover, prostaglandin E2 is a bioactive signaling molecule metabolized from phospholipid membranes through the enzymatic activity of cyclooxygenase-2 (COX-2). Similarly, COX-2 point mutation mice show altered morphology of cerebellar neuronal dendrites and dendritic spines, accompanied by ASD-like behaviors including social deficits, repetitive behaviors, and anxiety (Kissoondoyal et al., 2021).

5.2 Cerebellum-Specific Gene Knockout Leads to ASD-Like Phenotypes in Mice

To further validate the influence of the cerebellum on ASD, researchers have conducted systematic analyses using mouse models through cerebellum-specific gene deletion or mutation. Currently known cerebellum-specific gene knockouts that can induce ASD-like phenotypes in mice include TSC, PTEN, SHANK, CHD8, AUTS2, SCN8A, among others.

Tuberous sclerosis (TSC) is an autosomal dominant genetic disease that can cause benign tumors in the central nervous system and non-neural tissues. Studies have shown that TSC patients may be associated with cerebellar tubers, affecting cerebellar development and increasing ASD risk. TSC1 or TSC2 gene mutations affect the mTOR signaling pathway and are associated with ASD. In mouse models, both heterozygous and homozygous deletion of Tsc1 in cerebellar Purkinje cells can lead to ASD-like behaviors such as abnormal social interaction and repetitive behaviors (Tsai et al., 2012). Rapamycin treatment can prevent these behavioral abnormalities. These findings reveal the role of Tsc1 in cerebellar function and provide a new molecular basis for understanding cognitive disorders such as ASD.

PTEN (phosphatase and tensin homolog) plays an important role in cell growth, protein synthesis, and proliferation by inhibiting the PI3K/AKT/mTOR signaling pathway. Its function typically affects synaptic plasticity and neuronal cell structure (Tilot and Frazier et al., 2015). In mouse models, PTEN deletion or dysfunction is associated with neurological deficits and ASD-like behaviors, including altered social ability, repetitive behaviors, and anxiety phenotypes, which are relevant to human ASD (Clipperton-Allen & Page, 2020). Studies indicate that approximately 2-5% of children with ASD have PTEN gene mutations, and this proportion may be higher in ASD individuals with macrocephaly (Kaymakcalan et al., 2021), further demonstrating PTEN's status as a high-risk factor in ASD pathogenesis. PTEN deletion is typically lethal at the embryonic stage. Studies have found that cerebellum-specific PTEN deletion leads to motor coordination deficits, possibly related to hypertrophy of cerebellar granule cells. Deletion of PTEN in Purkinje cells (PTEN-KO PC) induces ASD-like features including reduced social ability, repetitive behaviors,

and motor learning deficits. Mutant Purkinje cells exhibit somatic hypertrophy, abnormal dendritic and axonal structures, reduced excitability, and disruption of parallel fiber and climbing fiber synapses, ultimately leading to delayed cell death. These results reveal a novel role for PTEN in Purkinje cell function and validate the close association between PTEN deletion and ASD-like pathologies. PTEN deletion in cerebellar astrocytes leads to Lhermitte-Duclos disease-like pathology and behavioral phenotypes, demonstrating PTEN's important role in regulating cerebellar cell growth and migration and its relevance to ASD-like behaviors (Chang-Hyuk Kwon & Charles G. Eberhart, 2001).

Studies have shown that deletion of PTEN in Purkinje cells (PTEN-KO PC) leads to phenotypic characteristics similar to ASD, including reduced social ability, repetitive behaviors, and motor learning deficits. Additionally, mutant Purkinje cells display somatic hypertrophy, abnormal dendritic and axonal structures, reduced excitability, and disruption of parallel fiber and climbing fiber synapses, ultimately resulting in delayed cell death. These research findings reveal a novel role for PTEN in Purkinje cell function and further validate the close association between PTEN deletion in Purkinje cells and the occurrence of ASD-like pathologies (Cupolillo et al., 2016).

SHANK family proteins are abundantly expressed in the cerebellum and play important roles in neuronal synapse formation, neuronal signal transmission, and regulation of cerebellar function (Uemura et al., 2004; Sato et al., 2012). SHANK1, SHANK2, and SHANK3 constitute a family of scaffold proteins that are part of the postsynaptic density (PSD) of glutamatergic synapses and serve to connect receptors with the actin cytoskeleton (Sala et al., 2015). SHANK1 and SHANK2 are abundantly expressed in Purkinje cells and their dendrites in the cerebellum, while SHANK3 is mainly expressed in granule cells (Bockers et al., 2004). Studies have found that specific knockout of SHANK2 in mouse Purkinje cells leads to ASD-like behaviors, including repetitive behaviors, impaired ultrasonic vocalizations, and balance deficits (Peter et al., 2016). This suggests that deletion of SHANK2 in cerebellar cells may be associated with ASD occurrence.

Chromodomain helicase DNA-binding protein 8 (CHD8) gene mutation is a high-risk factor for ASD. Its knockout in the mouse cerebellum may lead to cerebellar hypoplasia and motor coordination deficits, subsequently affecting social and behavioral phenotypes (Kawamura et al., 2021). Studies have found that cerebellar granule neuron progenitor-specific CHD8 knockout leads to abnormal phenotypes in social and light/dark tests (Chen et al., 2022). These findings emphasize the critical role of CHD8 in cerebellar development and are important for understanding the specific contribution of the cerebellum to ASD pathogenesis.

ASD susceptibility candidate gene 2 (AUTS2) is a risk gene associated with ASD that primarily affects brain development processes. AUTS2 is also widely expressed in the cerebellum (Bedogni et al., 2010), particularly localizing to Purkinje cells and Golgi cells during postnatal development. Studies have shown

that conditional knockout of AUTS2 in mice leads to reduced cerebellar volume, delayed Purkinje cell (PC) maturation, and abnormal synapse development. These mice also show significantly impaired abilities in motor learning and vocal communication, exhibiting cerebellar dysfunction characteristics associated with ASD (Yamashiro et al., 2020). Therefore, AUTS2 impairment may significantly impact functional cerebellar development and thus be associated with ASD pathogenesis.

Additionally, deletion of SCN8A expression in cerebellar Purkinje cells has been found to cause cerebellar degeneration and behavioral abnormalities associated with ASD. The SCN8A gene encodes voltage-gated sodium channel 8A, located on chromosome 12q13, containing 26 exons, and is widely expressed in neurons of the central and peripheral nervous systems. Its gene expression changes are closely related to the pathogenesis of various neurological diseases. SCN8A gene mutations often show autosomal dominant inheritance and are known to be associated with early-onset epileptic encephalopathy with intellectual disability. Research results show that mice with SCN8A knockout specifically in cerebellar Purkinje cells exhibit significant loss of cerebellar Purkinje cells and thinning of the molecular layer, leading to overall reduced cerebellar volume. Additionally, these mice show social impairments and deficits in motor coordination and motor learning in neurobehavioral assessments (Yang et al., 2022). Therefore, it can be speculated that deletion of SCN8A expression in the cerebellum may lead to behavioral abnormalities similar to ASD.

These research findings emphasize the important role of the cerebellum in ASD pathogenesis and provide key insights for understanding the neurobiological basis of ASD.

6. Summary and Outlook

There is a close association between abnormal cerebellar development and ASD. Although the specific pathophysiological mechanisms require further investigation, this association provides a new perspective for deeply understanding the pathogenesis of ASD. Key evidence obtained from both clinical research and rodent animal models in this review demonstrates that the cerebellum plays a critical role in the pathophysiology of ASD. The influence of different genetic or environmental factors may cause early cerebellar damage, which subsequently significantly alters the structure and function of cerebellar neural circuits, thereby triggering motor and cognitive functional impairments. As a widely connected component of neural circuits, the cerebellum works with other brain regions to regulate social and stereotyped behaviors in individuals with ASD. Thus, abnormal cerebellar development plays an important role in the occurrence and development of ASD (see Figure 1).

[Figure 1: see original paper] Schematic diagram of the relationship between abnormal cerebellar development and autism spectrum disorder

Currently, research and clinical trials targeting the cerebellum as a therapeutic

target for ASD are gradually emerging. Early studies indicate that improving cerebellar function and structure can significantly enhance social and cognitive functions in ASD patients. Neuromodulation and pharmacological interventions are considered potential approaches to improve ASD symptoms by regulating cerebellar neural circuit activity. Neuromodulation techniques such as deep brain stimulation and neural circuit modulation have shown certain efficacy in some ASD patients. These technologies intervene in cerebellar regions through electrical stimulation or neuromodulation devices to improve neural circuit function and integration, thereby alleviating core symptoms of ASD patients.

In the future, cerebellum-based personalized treatment strategies will be at the forefront of ASD therapy. With further understanding of cerebellar neural circuits and functions, future research will focus on developing more personalized and precise treatment strategies. Combining genomics and brain imaging technologies can accurately identify cerebellum-specific abnormal subtypes in ASD patients and select the most effective treatment approaches accordingly. Collaboration among interdisciplinary research teams will promote comprehensive analysis of the relationship between the cerebellum and ASD, and the integration of neuroscience, genetics, psychology, and clinical medicine will provide new perspectives and therapeutic pathways for understanding the complex neurodevelopmental mechanisms of ASD.

Of course, targeting the cerebellum as a therapeutic target for ASD has certain limitations. First, neurodevelopmental abnormalities associated with ASD involve complex interactions among multiple brain regions, and relying solely on cerebellar treatment may not comprehensively address the etiology and symptoms. Second, individual differences and heterogeneity among ASD patients mean that treatment effects targeting the cerebellum will vary, and the long-term efficacy and safety of current treatment strategies still require validation. Future research should continue to explore multi-factor treatment strategies, including personalized and comprehensive interventions considering multiple brain regions, to improve treatment efficacy and quality of life.

In summary, the cerebellum as a therapeutic target for ASD holds important theoretical and clinical significance. Future research will further explore the detailed role of the cerebellum in ASD pathogenesis and develop more precise and effective treatment strategies, providing new hope and opportunities for improving the quality of life of ASD patients.

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Note: Figure translations are in progress. See original paper for figures.