



The Role of Synaptic Dysfunction as a Key Driver in Autism Pathogenesis

Stefan Bittmann ^{a,b,++*}

^a Department of Pediatrics, Ped Mind Institute (PMI), Hindenburgring 4, D-48599 Gronau, Germany.

^b Shangluo Vocational and Technical College, Shangluo, 726000, Shaanxi, China.

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: <https://doi.org/10.9734/ajpr/2024/v14i11403>

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here:

<https://www.sdiarticle5.com/review-history/126641>

Short Communication

Received: 10/09/2024

Accepted: 13/11/2024

Published: 18/11/2024

ABSTRACT

Autism in childhood is a heterogeneous disease with around 110 phenotypes. Around 800 genes are affiliated with autism including members of neuro-ligand, neuroligin, cadherin, GABA receptors, SHANK gene families, mutated UBE3A on chromosome 15 and SNORD 116 precursor interaction. A predominant 4:1 male to female ratio is found in autistic spectrum disorder. 50 per cent of all autistic children show chromosome deletions and duplications, these are often found on the 15th and 16th chromosome. Copy number repeat variants in DNA are also well described in pathogenesis of autism patients. There is an overlap with other neurodevelopmental syndromes like tuberous sclerosis, Williams-syndrome, Phelan McDermid syndrome and Sphrintzen syndrome. The hypothesis of the term "atypical connectivity" in different brain regions with partial under- and overconnectivity with reduced brain networking at the psychosocial level was described. Different hypothesis about the origin of autism in children were described. The hypothesis of early lack of basic trust, mercury intoxication and different aspects concerning the origin of this extraordinary

⁺⁺ Professor (Visit. Prof.);

*Corresponding author: Email: stefanbittmann@gmx.de;

Cite as: Bittmann, Stefan. 2024. "The Role of Synaptic Dysfunction As a Key Driver in Autism Pathogenesis". *Asian Journal of Pediatric Research* 14 (11):55-67. <https://doi.org/10.9734/ajpr/2024/v14i11403>.

disease of 2 percent of children were stated but not confirmed to date. Especially low immature production of IgF-1 by oligodendrocytes in the corpus callosum leads to slowing of the PI3K/AKT chain activation of myelination that Ig-F1 could play an important role in the origin of the disease. Synaptic dysfunction with hypomyelination and impaired impulse transmission seem to play an extraordinary role with under- and overconnectivity with reduced brain networking at the psychosocial level in autistic children. Functional underconnectivity is found in 5 different brain areas, prefrontal, parieto-occipital, motor, somatosensory and the temporal region. Functional overconnectivity is often present in temporo-thalamic regions. Recent research shed light on synaptic dysfunctions with disrupted normal impulse signaling. In this review the different neurochemical findings and the correlation of synaptic dysfunction in autistic children will be closely evaluated.

Keywords: Autism; child; synapsis; atypical connectivity; synaptopathy.

1. INTRODUCTION

Autism spectrum disorder is a profound developmental disorder that is based on complex disorders of the central nervous system, especially in the area of perception processing, and begins in childhood (Johnson et al. 2007). At its core is a severe disorder of relationships and communication (Madson et al. 2014). The effects of the disorder hinder relationships with the environment in various ways, participation in community life, and the ability to integrate into society, as both cognitive and language, motor, emotional, and interactional functions are affected (Williams et al. 1999). In addition, numerous behavioral abnormalities, which can be particularly burdensome for caregivers in everyday interactions with autistic individuals, are present (Samanta et al. 2022). Autistic individuals are typically multiply disabled. As with all multiple disabilities, the focus of the disability shifts over the course of development with age (Lee et al. 2024). Following characteristics are listed as defining features of early childhood autism, in addition to the early onset as qualitative impairments in interpersonal relationships; impairments in communication and imagination and a significantly restricted repertoire of activities and interests. Children with autism may initially not understand gestures, smiles, or words. They are unable to establish a normal relationship with other people, even with their own parents (Williams et al. 1999). They withdraw, isolate themselves autistically. Children with autism cannot play "normally" and use their toys in the same, often misappropriated way. They develop stereotypes: spinning and twirling wheels, sifting sand, waving threads or paper (Lisk et al. 2024). The main symptoms of autistic disorder vary in their severity. People with autism often have problems with eating and sleeping from infancy and develop self-stimulating behaviors that can range

from self-injury to severe external aggression (Kotagal et al. 2024). They often insist on very specific orders or can drive their caregivers to despair through excessive collecting of certain objects, refusal to wear certain clothing, repetition of the same behaviors or verbal expressions (Williams et al. 1999). Many have no sense of danger. A large proportion of autistic individuals do not learn to speak. The intellectual abilities of people with autism vary greatly. They range from intellectual disability to normal intelligence, with some of them showing remarkable partial achievements in mathematics, technical disciplines, music, and other areas (Johnson and Myers 2007). According to current knowledge, 5-15 people with autistic disorders per 10,000 individuals in the population in Germany were found. Boys are affected by the disorder four times more often than girls (Johnson and Myers 2007). Early childhood autism can be found in families of all nationalities and social classes (Johnson and Myers 2007). Despite extensive research results, there is still no explanatory model that can fully and conclusively demonstrate the causes of autistic disorder. According to current knowledge, autism is not curable but treatable. As diverse as the manifestations of autistic disorder are, the pedagogical and therapeutic approaches must be equally diverse and tailored to each individual with autism. Through targeted autism-specific support and therapy measures, a significant improvement in symptoms can be achieved in many cases, increasing the quality of life for both the autistic individual and their caregivers. Recent research has highlighted the origin of autistic disorders as a synaptopathy, where excitatory synapses are more prominent than inhibitory synapses (Fatemi et al. 2024). The exact mechanism on synaptical function and formation is to date not completely understood.

2. THE ROLE OF SYNAPTIC TRANSMISSION IN AUTISTIC DISORDERS

2.1 Physiology of Synapses and Synaptogenesis

Synapse refers to the site of a neuronal connection through which a nerve cell is in contact with another cell like a sensory cell, muscle cell, gland cell, or another nerve cell. Synapses serve the transmission of excitation, but also allow the modulation of signal transmission, and they are capable of storing information through adaptive changes. The number of synapses in the brain of an adult is approximately 100 trillion (10^{14}) - in terms of a single neuron, it ranges between 1 and 200,000. The term synapse was coined in 1897 by Charles S. Sherrington for the connection between neurons, for example between the branched end of the axon of a nerve cell and the branched dendrites of another nerve cell. In most cases, they are chemical synapses. In these synapses, the signal that arrives as an electrical action potential is converted into a chemical signal, carried in this form across the synaptic cleft between the cells, and then transformed back into an electrical signal. The sending cell (presynaptic) releases neurotransmitters, chemical messengers, which bind to membrane receptors of the receiving cell on the other side of the cleft. This anatomically determines the direction of signal transmission (only forward), which is fundamental for information processing in neuronal networks. The excitatory transmitter is either produced in the axon terminal of the sending neuron or synthesized in its cell body and transported axonally to the presynaptic membrane regions. In contrast, electrical synapses are gap junctions, contact points where ion channels of two cells are directly coupled, allowing the passage of ions and small molecules from one cell to another. Initially, such synapses were discovered between neurons, but similar contact points are also found in other tissues, including plants. In a figurative sense, immunological synapses refer to the sites of temporary cellular contacts between cells of the immune system, both among themselves and with cells of the surrounding tissue. Molecules on the surface of one cell bind to receptor molecules and adhesion molecules in the cell membrane of the other, exchanging information. In a synaptic end bulb, the incoming action potential, during the depolarization phase - in addition to the

transient opening of sodium and slightly delayed potassium ion channels - leads to the temporary opening of voltage-gated calcium ion channels and thus a brief influx of calcium ions. The increased intracellular calcium causes the release of a neurotransmitter into the synaptic cleft within a few milliseconds. In the end bulb, this neurotransmitter is stored in special synaptic vesicles and provided near the cell membrane in synaptic vesicles, which can fuse with the presynaptic membrane under the influence of calcium and then release the transmitter molecules outward. This process, also called exocytosis, is made possible by the conformational change of calcium-binding proteins, especially synaptotagmins. They initiate the formation of a protein complex of SNARE proteins - from a synaptobrevin in the vesicle membrane on one hand and on the other hand a syntaxin and two SNAP proteins in the cell membrane - which allows the fusion of both membranes. Other proteins are then involved in causing the fused vesicle to open outward and, for example, accelerate the release of neurotransmitters, such as Complexin I and II. Subsequently, a certain number of synaptic vesicles are provided at the axolemma again via synapsin. On the other side of the synaptic cleft, specific receptor molecules for the neurotransmitter are found in the postsynaptic, subsynaptic, membrane of the target cell. These receptors are usually associated with ligand-gated ion channels (ionotropic), so that an ion channel can open immediately when the transmitter molecule binds to the appropriate receptor. Depending on the type of ion for which this channel is permeable, the membrane potential in the postsynaptic region is either raised (EPSP) or lowered (IPSP) by the ion current. Depending on the receptor type, an indirect second messenger cascade can also be triggered (metabotropic), which can also lead to a change in membrane potential and possibly trigger further processes in the postsynaptic cell. Through the respective intracellular messenger, signal amplification can also be induced, but with a delayed effect. The transmitter molecules do not bind irreversibly but detach from their receptor after a certain time. In the synaptic cleft or extracellular space, they are often broken down by specific enzymes (such as acetylcholinesterase), limiting their effect. For some transmitters, there is no breakdown, but they are taken back into the presynaptic terminal or cleared by glial cells. The signals transmitted through chemical synapses have a biochemically defined effect. Depending on the equipment of

the postsynaptic membrane influenced by the sending neuron, either an excitatory or inhibitory effect is achieved. Not only individual synapses, but entire neurons are therefore classified into excitatory and inhibitory, depending on whether they form only excitatory or only inhibitory synapses on target cells. For a target cell within the central nervous system, it is usually the case that it receives signals from different neurons, including opposing ones, and that the electrical voltage changes they trigger add up. If the sum of the incoming excitatory and inhibitory (postsynaptic) voltage changes at the axon hillock of this nerve cell exceeds a certain threshold during the potential change, the cell itself becomes active, generates an action potential, and transmits it further along its axon. In a variety of psychiatric and neurological disorders, it is assumed that synaptic transmission pathways are disrupted. There are indications of a link between various forms of depression and disturbances in signal transmission through the neurotransmitter serotonin. Numerous medications or toxins exert their effects by interacting with steps of transmission at synapses (beta-blockers, nicotine, atropine, hyoscyamine, parathion, cocaine, and many more). The majority of synapses operate with chemical information transmission, but in some cases, there is also direct electrical conduction. In these electrical synapses, the action potential is passed directly to the next cell without intermediary neurotransmitters. In many electrical synapses, there are connection channels through the cell membrane, called "gap junctions," through which the intracellular spaces of adjacent cells are directly coupled. These gap junctions are pores in the cell membrane formed by specific proteins called connexins. Six connexin molecules line the pore of a cell, together forming a connexon. Contact between two connexons of neighboring cells creates a channel that crosses both membranes and connects them. The open connection allows diffusion of even medium-sized molecules, such as secondary messengers, and enables a very rapid transmission of changes in membrane potential with relatively low electrical resistance through ion passages. Such electrical synapses occur, for example, between neurons in the retina; they are also found between glial cells and especially between cells of the heart muscle, allowing them to act synchronously as a single unit electrically, similar to smooth muscle like the uterus. Another form of electrical excitation transmission is capacitive coupling through a large, close

membrane contact, as found, for example, in the human ciliary ganglion. Excitatory and inhibitory synapses could play an important role in the origin of autism in children. Synaptogenesis is the formation of synapses between neurons in the nervous system, with a surge in synapse formation during early brain development. It is crucial during the critical period for neural growth and synaptic pruning. The neuromuscular junction (NMJ) is a well-studied synapse composed of a motor neuron, myofiber, and Schwann cell. The motor neuron releases acetylcholine to trigger muscle contraction. Astrocytes play a role in synapse plasticity. During development, myoblasts, motoneurons, and Schwann cells originate from different embryonic regions. Axons are guided by growth cones to form contacts with myotubes. Synapse development at the NMJ shows specific patterning with midpoints being innervated. Post-synaptic differentiation involves increased AChR concentration through clustering and gene regulation. Pre-synaptic differentiation involves changes in synaptic volume and vesicle clustering. Synaptic maturation involves synapse elimination, where multiple inputs are reduced to one. Synapse formation specificity distinguishes between fast and slow-twitch muscle fibers. In the CNS, synaptogenesis shares similarities with the NMJ but involves different neurotransmitters and receptors. Factors regulating CNS synaptogenesis include signaling molecules, morphology, and environmental enrichment. The Wnt protein family contributes to synapse formation in the CNS and NMJ. In the CNS, Wnts induce presynaptic and postsynaptic terminal formation in various neuronal cell types. Wnts play a role in AChR clustering and growth cone enlargement. Wnt expression is essential for synaptic development and plasticity in both systems. Synapses segregate as they mature, with all axonal inputs except one retracting. The post-synaptic end plate deepens and forms folds to increase neurotransmitter reception. Schwann cells transition from loose covers to myelinated caps over the neuromuscular junction.

2.2 Pre-synaptic and Post-synaptic Differentiation

Changes in the developing axon terminal include increased synaptic volume, vesicle clustering, and membrane polarization. Neurotrophins and cell adhesion molecules released from muscle cells mediate these changes. Following contact with the motoneuron, the myotube shows an increased concentration of AChR in the synapse,

enhancing synaptic signal transmission. This is achieved through clustering of AChR, up-regulation of AChR gene transcription in post-synaptic nuclei, and down-regulation in non-synaptic nuclei. The initiation of post-synaptic differentiation may be triggered by neurotransmitters or changes in the extracellular matrix.

2.3 Synapse-specific Transcription, Extrasynaptic Repression and Synapse Elimination

Axonal signals regulate gene expression in myonuclei beneath the synapse, leading to localized up-regulation of AChR gene transcription. CGRP and neuregulin released by the axon activate kinases that enhance AChR gene transcription. Activity-dependent repression of AChR gene in non-synaptic nuclei occurs due to the electrical signal generated by the synapse. This ensures AChR localization to the synapse, enhancing signal fidelity. Synaptic pruning involves competition between axons, with stronger synapses maintained through synaptotrophins and weaker ones eliminated. Synaptotoxins released from depolarized post-synaptic membranes deter weaker axons.

Different Neurochemical Findings in Autistic Setting: Different neurochemical findings were found in autistic children and evaluated in detail in former studies concerning finding the origin of autism.

Increase of excitatory and decrease of inhibitory synapses: In autism, there is an increase in excitatory synapses and a decrease in inhibitory synapses in the prefrontal cortex (37,42). Previous research has shown that there are more excitatory pyramidal cells and fewer inhibitory parvalbumin+ chandelier interneurons in the prefrontal cortex of individuals with autism (37,42,46). The overall impact of these changes on synaptic abundance in the cortex remains unclear. In a recent study, researchers examined the number of excitatory and inhibitory synapses in the prefrontal cortex of 10 postmortem brains from individuals with autism and 10 control cases (37,42,46). Excitatory synapses were identified using VGlut1 and postsynaptic density protein-95 markers, while inhibitory synapses were identified using vesicular gamma-aminobutyric acid transporter and gephyrin markers. The analysis revealed an increase in excitatory synapses in upper cortical layers and a decrease in inhibitory synapses across all cortical layers in

autism brains compared to controls (37,42,46). These alterations in synaptic numbers may contribute to neuronal dysfunction and disrupted network connectivity in the prefrontal cortex of individuals with autism (37,42,46).

Low IgF-1 Production in oligodendrocytes in the Corpus Callosum: Slowing of PI3K/AKT chain activation of myelination; early prevention of autism could be achieved by measuring IgF-1 in umbilical cord blood at delivery (52). This leads to synaptic dysfunction with hypomyelination and disturbed impulses (52).

2.4 Loss of Protein Tyrosine Phosphatase Receptor Delta (Ptpd)

The brain cortex plays a crucial role in higher-level cognitive functions, and disruptions during cortical development can lead to lasting consequences and are linked to brain disorders (Cortes et al. 2024). Previous research has shown that the protein tyrosine phosphatase receptor delta (Ptpd), associated with various neurodevelopmental disorders, is vital for cortical brain development (Cortes et al. 2024). Loss of Ptpd expression results in an abnormal increase in excitatory neurons in mice by overactivating pro-neurogenic receptors TrkB and PDGFR β in neural precursor cells (Cortes et al. 2024). A recent study aimed to investigate the long-term effects of these alterations in adulthood (Cortes et al. 2024). This study revealed that in Ptpd $^{+/-}$ or Ptpd $^{-/-}$ mice, the excessive excitatory neurons persisted into adulthood, impacting excitatory synaptic function in the medial prefrontal cortex (Cortes et al. 2024). Ptpd heterozygosity or homozygosity led to an increase in inhibitory GABAergic neurons in the cortex and impaired inhibitory synaptic transmission (Cortes et al. 2024). Furthermore, Ptpd $^{+/-}$ or Ptpd $^{-/-}$ mice exhibited autistic-like behaviors without learning and memory deficits or anxiety. The findings suggest that the loss of Ptpd has enduring effects on cortical neuron numbers and synaptic function, potentially influencing ASD-like behaviors (Cortes et al. 2024).

2.5 Mutation of Neuroligin-3-R451C

The gut's intrinsic nervous system interacts with gut-associated lymphoid tissue (GALT) through neuroimmune interactions. The caecum, a crucial region of the gastrointestinal tract, plays a role in immune responses and microbial regulation. Individuals with Autism Spectrum Disorder (ASD)

often experience gastrointestinal issues, including inflammatory disorders. Mutations in genes like neuroligin-3 (NL3) are linked to autism and synaptic transmission impairments. NL3R451C mice, a model of autism, show altered enteric neurons and GI dysfunction. Researchers investigated the impact of the R451C mutation on the caecal nervous system and immune function (Sharna et al. 2020). NL3R451C mice had reduced caecal weight and increased neuron density, particularly NO-producing neurons (Sharna et al. 2020). The density of Iba-1 labeled macrophages in the caecal patch was higher in NL3R451C mice, with smaller and more spherical morphology. These findings highlight the effects of the autism-associated Nlgn3 mutation on neural and immune pathways (Sharna et al. 2020).

Reduced number of Chandelier cells: Chandelier (Ch) cells are a type of cortical interneuron characterized by axon terminal structures called cartridges that form synapses on the axon initial segment of excitatory pyramidal neurons. Previous research suggests that individuals with autism have a lower number of Ch cells and reduced GABA receptors in the Ch cell synaptic targets in the prefrontal cortex (Hong et al. 2023). To further investigate Ch cell alterations, researchers compared the length of cartridges and the number, density, and size of Ch cell synaptic boutons in the prefrontal cortex of individuals with autism and control subjects and analyzed postmortem samples of the human prefrontal cortex (Brodmann Areas 9, 46, and 47) from 20 individuals with autism and 20 age- and sex-matched controls (Hong et al. 2023). Ch cells were identified using an antibody against parvalbumin, a marker that labels soma, cartridges, and synaptic boutons. The results showed no significant differences in the average length of cartridges or the total number or density of boutons between control subjects and those with autism. Researchers observed a significant decrease in the size of Ch cell boutons in individuals with autism. This reduction in bouton size may lead to decreased inhibitory signal transmission and affect the balance of excitation to inhibition in the prefrontal cortex in autism (Hong et al. 2023).

Microglial Tmem59-Deficiency: Synaptic abnormalities are a key feature of autism spectrum disorders and contribute to behavioral issues in these disorders. Microglia, the brain's immune cells, are involved in synapse refinement. Dysregulated synaptic pruning by

microglia during brain development has been linked to ASDs, but the exact mechanism is not fully understood. We found that the expression of Transmembrane protein 59 (TMEM59), which regulates microglial function, is reduced in autistic patients (Meng et al. 2023). Mice lacking TMEM59, either completely or specifically in microglia, displayed ASD-like behaviors (Meng et al. 2023). These mice also showed increased excitatory synaptic transmission, dendritic spine density, and levels of excitatory synaptic proteins (Meng et al. 2023). TMEM59-deficient microglia had impaired synapse engulfment ability both in vivo and in vitro. Researchers from China discovered that TMEM59 interacts with the C1q receptor CD93, and TMEM59 deficiency leads to CD93 protein degradation in microglia, impairing synapse engulfment (Meng et al. 2023). This study highlights the role of TMEM59 in regulating microglial function in synapse refinement during brain development and suggests that TMEM59 deficiency may contribute to ASDs by disrupting synapse phagocytosis and altering neuronal activity balance (Meng et al. 2023).

CHD8-gene loss on genome organization: Whole-exome sequencing of individuals with autism spectrum disorder (ASD) and their unaffected family members has identified CHD8 as a frequently mutated gene (Shi et al. 2023). However, the impact of CHD8 loss on genome organization and neuronal function remains poorly understood. In a recent study, researchers generated human embryonic stem cell lines with CHD8 mutations and observed altered gene expression in differentiated cortical neurons, particularly affecting neural development and synaptic transmission (Shi et al. 2023). CHD8^{+/-} neurons exhibited reduced firing rates and synaptic activity, which could be rescued by CHD8 overexpression. Additionally, CHD8^{+/-} neurons showed increased chromatin accessibility, particularly near the AUTS2 gene implicated in ASD. The genes affected in CHD8^{+/-} neurons overlap with those mutated in ASD, intellectual disability, and schizophrenia, highlighting the potential role of CHD8 in these disorders. The study provided insights into the molecular and functional consequences of CHD8 mutations in neurons (Shi et al. 2023).

Defects in syntabulin-mediated synaptic cargo transport: The formation and maintenance of synapses rely on the delivery of synaptic proteins from the soma to distal synapses. Impaired transport may be linked to neurodevelopmental disorders like autism (Xiong

et al. 2020). Syntabulin acts as a motor adapter for kinesin-1 and presynaptic cargos (Xiong et al. 2020). Defects in syntabulin-mediated transport lead to reduced synapse formation and maturation, contributing to autism-like synaptic dysfunction and social behavioral abnormalities (Xiong et al. 2020). Syntabulin expression peaks in early postnatal development and declines with brain maturation. Neurons lacking syntabulin show impaired transport, reduced synapse density, altered synaptic transmission, and behavioral abnormalities resembling autism traits. A human missense variant of syntabulin found in an autism patient fails to rescue synaptic deficits in mice lacking syntabulin (Xiong et al. 2020). This important study suggests that impaired transport mechanisms contribute to synaptic dysfunction and behavioral abnormalities in autism (Xiong et al. 2020).

Changes in metabotropic glutamate receptor (mGluR) signaling:

Various neurodevelopmental disorders are associated with changes in metabotropic glutamate receptor (mGluR) signaling, which plays a crucial role in synaptic plasticity, spine maturation, and circuit development. In one study published in Nature Communications in 2019, Edfawy et al. explored the function of Gprasp2, a gene implicated in neurodevelopmental disorders that is involved in sorting G-protein-coupled receptors after endocytosis (Edfawy et al. 2019). Deleting Gprasp2 in mice results in ASD-like behavior and synaptic communication alterations (Edfawy et al. 2019). Modulating Gprasp2 levels affects mGluR5 surface availability, impacting dendritic complexity, spine density, and synaptic maturation bidirectionally (Edfawy et al. 2019). Gprasp2 loss enhances hippocampal long-term depression, indicating increased mGluR-dependent activation. These findings highlight Gprasp2's role in glutamatergic synapses and provide insights into its association with neurodevelopmental disorders (Edfawy et al. 2019).

KMT5B deficiency in prefrontal cortex: Large-scale genetic screening has identified KMT5B (SUV420H1) as a high-risk gene for autism due to its role as a histone (Wang et al. 2021). H4 K20 di- and tri-methyltransferase highly expressed in the prefrontal cortex (PFC) (Wang et al. 2021). However, the specific biological function of KMT5B in the brain and its connection to autism are not well understood. In another recent study, researchers investigated the effects of Kmt5b deficiency in the PFC on behavior,

synaptic transmission, and molecular mechanisms (Wang et al. 2021). Mice with Kmt5b deficiency in the PFC exhibited social deficits, a hallmark of autism, without affecting other behaviors. Additionally, Kmt5b deficiency led to impaired glutamatergic synaptic transmission in the PFC, accompanied by reduced expression of glutamate receptor subunits and associated proteins. The reduction of H4K20me2 due to Kmt5b deficiency hindered 53BP1-mediated DNA repair, resulting in increased p53 expression and upregulation of the gene Ddit4 (Redd1), which is linked to synaptic impairment (Wang et al. 2021). RNA-sequencing data revealed that Kmt5b deficiency upregulated genes involved in cellular stress response and ubiquitin-dependent protein degradation. The findings of this study highlighted the critical role of Kmt5b in the PFC and suggest that its deficiency may contribute to autistic phenotypes through synaptic dysfunction and transcriptional dysregulation (Wang et al. 2021).

SCN2A deficiency: Microglia, the brain's immune cells, play a crucial role in regulating brain development and homeostasis. Recent genetic studies have identified SCN2A deficiency as a leading cause of ASD and intellectual disability (Wu et al. 2024). A mouse model with Scn2a deficiency shows behavioral and neuronal abnormalities, with microglia playing a role in synaptic pruning (Wu et al. 2024). In humans, a cerebral organoid model with an SCN2A mutation also shows increased synaptic elimination by microglia. This recent important study highlights the importance of microglia in ASD models from mice to human cells (Wu et al. 2024).

Over-pruning Hypothesis: Another study presents the over-pruning hypothesis of autism, which suggests that overly aggressive synaptic pruning in infancy and early childhood may contribute to the development of autism (Thomas et al. 2016). The hypothesis aims to explain the heterogeneity in the timing of ASD manifestation, including early onset, late onset, and regression. Computer simulations support this hypothesis by showing how unaffected siblings of individuals with ASD may inherit a milder version of the pathological mechanism or co-inherit risk factors without the mechanism. The hypothesis predicted that early development in ASD will initially appear typical and that sensory and motor issues will precede social difficulties (Thomas et al. 2016). Emerging longitudinal

studies provide some support for these predictions. This study reviews evidence supporting the over-pruning hypothesis, its relation to other theories, and its implications for understanding the broader autism phenotype. The hypothesis integrates data from various disciplines, including behavioral studies, neuroscience, genetics, and interventions (Thomas et al. 2016).

WDR62-deficiency: Abnormal brain size is linked to a higher incidence of autism spectrum disorder (ASD) in children (Xu et al. 2022). Genetic studies have identified mutations in the WD repeat domain 62 (WDR62) gene as a factor in ASD (Xu et al. 2022). Recent research demonstrated that mice lacking *Wdr62* showed reduced brain size, learning and memory deficits, and ASD-like behaviors (Xu et al. 2022). Interestingly, mice with *Wdr62* depletion in mature neurons had normal brain size but displayed abnormal social interactions and repetitive behaviors (Xu et al. 2022). WDR62 played a role in regulating dendritic spine formation and synaptic transmission in brain cells. Treatment with retinoic acid improved ASD-like behaviors in mice with WDR62 deficiency by modulating the expression of ASD and synaptic genes. These findings offer insights into the connection between WDR62 gene mutations and ASD, which could inform better diagnosis and treatment strategies for ASD (Xu et al. 2022).

3. DISCUSSION

Autism Spectrum Disorder (ASD) affects about 1/36 of the global child population and is characterized by social interaction challenges, communication difficulties, repetitive behaviors, and focused interests. The causes of autism are largely unknown and heterozygous, leading to suboptimal care for affected individuals (Johnson et al. 2007). To gain a better understanding of autism, studying postmortem brain tissue is of utmost importance (Graham et al. 2020). Studying brain tissue directly is essential because the pediatric brain is the primary organ affected by autism (Graham et al. 2020). It provides insights into cellular organization, connectivity, neurotransmitter systems, and brain plasticity, which are key to understanding the condition's development and potential treatments (Graham et al. 2020). Brain tissue research allows for histological analysis to identify neural network abnormalities, gene expression studies to understand genetic regulation in the autistic brain, and biochemical analysis to uncover

changes in brain biochemistry. In brain postmortem studies of autism patients an increased serotonin axons with higher immunoreactivity to 5-HT transporters were described (Azmitia et al. 2011). However, researchers face challenges such as limited availability of brain tissue for study and the lack of comprehensive medical information about donors. Overcoming these challenges is crucial to advancing our understanding of autism and taking all neurochemical findings in various studies into account. In recent years, research efforts concentrate on pathological synaptic formation as the key driver of pathogenesis in autism spectrum disorders. Synaptogenesis refers to the formation or creation of new synapses on a nerve cell. Synaptogenesis, along with synapse elimination, is the basis for the lifelong plasticity of the brain. The majority of nerve cells or neurons develop prenatally through cell division and subsequent migration. Synaptogenesis is particularly dominant in the last third of pregnancy and in the postnatal phase. At birth, humans already have 100 billion neurons. These neurons establish connections to each other through synapses, initially creating many more synapses than are actually needed. This is followed by an experience-dependent elimination of synapses. Synapse formation and elimination reach their peak at different times, depending on the brain region. For example, the peak of synapse formation in the visual cortex occurs in the first year of life. The frontal cortex, responsible for action planning among other functions, only adequately forms synapses during the preschool years, and this process can continue into adolescence. Recent studies have evaluated a dysbalance between excitatory and inhibitory synapses that are the key driver for autistic development (Vakilzadeh et al. 2024). Nevertheless, there are many different additional findings in autism like a low Ig-F1 production in oligodendrocytes in the corpus callosum, leading to a slowing of PI3K/AKT chain activation of myelination (Velmeshev et al. 2019). Moreover, loss of protein tyrosine phosphatase receptor delta (*Ptprd*), mutations of *Neurologin-3-R451C*, a reduced number of Chandelier cells and defects of the syntabulin-mediated synaptic cargo transport were described in different studies (Cortes et al. 2024, Hong et al. 2023, Meng et al. 2022, Xiong et al. 2021, Wu et al. 2024, Xu et al. 2022, Sharna et al. 2022, Dingwall et al. 2024, Li et al. 2024). Other studies revealed synaptic abnormalities with microglial *Tmem59*-deficiency, *KMT5b* deficiency in prefrontal cortex, *SCN2A* deficiency and WDR62 deficiency (Meng et al.

2023, Wang et al. 2023, Wu et al. 2024, Xu et al. 2022). Recent studies focus on an over-pruning hypothesis, abnormal changes in metabotropic glutamate receptor (mGluR) signaling and CHD8-gene loss on genome organization (Shi et al. 2023, Edfawy et al. 2019, Thomas et al. 2016).

4. CONCLUSIONS

Different heterogenous neurochemical findings were found in autistic children. Recent studies have evaluated a dysbalance between excitatory and inhibitory synapses that are the key driver for autistic development. The mechanisms responsible for synaptic cargo trafficking are not fully understood, but adaptor molecules play a crucial role in transport specificity. Disruptions in synaptic receptor trafficking may contribute to neurological and psychiatric diseases like autism. In conclusion, neurochemical findings in autistic patients and studies are heterogenous, whereas recent molecular research highlighted the importance of synaptic transmission formation disturbances in autistic children. Further intensive research is of great importance to develop therapeutical targets or gene therapeutical approaches for the future for these high population of autistic spectrum disorders in childhood.

5. FUTURE DIRECTION

Research must focus on closer evaluating molecular research on adaptor molecules, synaptic transmission formation and synaptic cargo transport in children with autism.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER

This paper is an extended version of a preprint document of the same author.

The preprint document is available in this link: <https://www.preprints.org/manuscript/202410.2314/v1>

[As per journal policy, preprint /repository article can be published as a journal article, provided it is not published in any other journal]

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

- Ahlqvist, V. H., Sjöqvist, H., Dalman, C., Karlsson, H., Stephansson, O., Johansson, S., Magnusson, C., Gardner, R. M., & Lee, B. K. (2024). Acetaminophen use during pregnancy and children's risk of autism, ADHD, and intellectual disability. *JAMA*, 331(14), 1205–1214. <https://doi.org/10.1001/jama.2024.3172>
- Anixt, J. S., Ehrhardt, J., & Duncan, A. (2024). Evidence-based interventions in autism. *Pediatric Clinics of North America*, 71(2), 199–221. <https://doi.org/10.1016/j.pcl.2024.01.001>
- Anixt, J. S., Ehrhardt, J., & Duncan, A. (2024). Evidence-based interventions in autism. *Pediatric Clinics of North America*, 71(2), 199–221. <https://doi.org/10.1016/j.pcl.2024.01.001>
- Azmitia, E. C., Singh, J. S., & Whitaker-Azmitia, P. M. (2011). Increased serotonin axons (immunoreactive to 5-HT transporter) in postmortem brains from young autism donors. *Neuropharmacology*, 60(7-8), 1347–1354. <https://doi.org/10.1016/j.neuropharm.2011.02.002>
- Bertoglio, K., & Hendren, R. L. (2009). New developments in autism. *Psychiatric Clinics of North America*, 32(1), 1–14. <https://doi.org/10.1016/j.psc.2008.10.004>
- Bourgeron, T. (2007). The possible interplay of synaptic and clock genes in autism spectrum disorders. *Cold Spring Harbor Symposia on Quantitative Biology*, 72, 645–654. <https://doi.org/10.1101/sqb.2007.72.020>
- Bruinsma, Y., Koegel, R. L., & Koegel, L. K. (2004). Joint attention and children with autism: A review of the literature. *Mental Retardation and Developmental Disabilities Research Reviews*, 10(3), 169–175. <https://doi.org/10.1002/mrdd.20036>

- Burnham Riosa, P., Khan, M., & Weiss, J. A. (2019). Measuring therapeutic alliance in children with autism during cognitive behavior therapy. *Clinical Psychology & Psychotherapy*, 26(6), 761–767. <https://doi.org/10.1002/cpp.2404>
- Carbone, P. S., Stipelman, C. H., Villalobos, M. E., Ellzey, A., Stuart, A., Stoddard, G. J., & Campbell, K. (2024). A comparison of parent-reported severe autism with mild/moderate autism among U.S. children. *Journal of Developmental and Behavioral Pediatrics*, 45(5), e422–e430. <https://doi.org/10.1097/DBP.0000000000001306>
- Cortés, B. I., Meza, R. C., Ancatén-González, C., Ardiles, N. M., Aránguiz, M. I., Tomita, H., Kaplan, D. R., Cornejo, F., Nunez-Parra, A., Moya, P. R., Chávez, A. E., & Cancino, G. I. (2024). Loss of protein tyrosine phosphatase receptor delta PTPRD increases the number of cortical neurons, impairs synaptic function and induces autistic-like behaviors in adult mice. *Biological Research*, 57(1), 40. <https://doi.org/10.1186/s40659-024-00522-0>
- Crane, L., Jones, L., Prosser, R., Taghrizi, M., & Pellicano, E. (2019). Parents' views and experiences of talking about autism with their children. *Autism*, 23(8), 1969–1981. <https://doi.org/10.1177/1362361319836257>
- Dingwall, R., May, C., Letschert, J., Renoir, T., Hannan, A. J., & Burrows, E. L. (2024). Attenuated responses to attention-modulating drugs in the *Neuroigin-3* R451C mouse model of autism. *Journal of Neurochemistry*, 168(9), 2285–2302. <https://doi.org/10.1111/jnc.16187>
- Edfawy, M., Guedes, J. R., Pereira, M. I., Laranjo, M., Carvalho, M. J., Gao, X., Ferreira, P. A., Caldeira, G., Franco, L. O., Wang, D., Cardoso, A. L., Feng, G., Carvalho, A. L., & Peça, J. (2019). Abnormal *mGluR*-mediated synaptic plasticity and autism-like behaviours in *Gprasp2* mutant mice. *Nature Communications*, 10(1), 1431. <https://doi.org/10.1038/s41467-019-09382-9>
- Enav, Y., Erhard-Weiss, D., Kopelman, M., Samson, A. C., Mehta, S., Gross, J. J., & Hardan, A. Y. (2019). A non-randomized mentalization intervention for parents of children with autism. *Autism Research*, 12(7), 1077–1086. <https://doi.org/10.1002/aur.2108>
- Fatemi, S. H., Eschenlauer, A., Aman, J., Folsom, T. D., & Chekouo, T. (2024). Quantitative proteomics of dorsolateral prefrontal cortex reveals an early pattern of synaptic dysmaturation in children with idiopathic autism. *Cerebral Cortex*, 34(13), 161-171. <https://doi.org/10.1093/cercor/bhae044>
- Gómez-Espinosa, A., Moreno, J. C., & Pérez-de la Cruz, S. (2024). Assisted robots in therapies for children with autism in early childhood. *Sensors (Basel)*, 24(5), 1503. <https://doi.org/10.3390/s24051503>
- Graham, S. F., Turkoglu, O., Yilmaz, A., Ustun, I., Ugur, Z., Bjorndhal, T., Han, B., Mandal, R., Wishart, D., & Bahado-Singh, R. O. (2020). Targeted metabolomics highlights perturbed metabolism in the brain of autism spectrum disorder sufferers. *Metabolomics*, 16(5), 59. <https://doi.org/10.1007/s11306-020-01685-z>
- Habayeb, S., Inge, A., Myrick, Y., Hastings, A., Long, M., Hoffman, S. B., Parker, S., Theodorou, P., Soutullo, O., Beers, L., & Godoy, L. (2023). A multisystem approach to improving autism care. *Pediatrics*, 152(5), e2022060584. <https://doi.org/10.1542/peds.2022-060584>
- Hernández-Díaz, S., Straub, L., Bateman, B. T., Zhu, Y., Mogun, H., Wisner, K. L., Gray, K. J., Lester, B., McDougale, C. J., DiCesare, E., Pennell, P. B., & Huybrechts, K. F. (2024). Risk of autism after prenatal topiramate, valproate, or lamotrigine exposure. *New England Journal of Medicine*, 390(12), 1069–1079. <https://doi.org/10.1056/NEJMoa2309359>
- Hong, T., McBride, E., Dufour, B. D., Falcone, C., Doan, M., Noctor, S. G., & Martínez-Cerdeño, V. (2023). Synaptic boutons are smaller in chandelier cell cartridges in autism. *PLOS ONE*, 18(4), e0281477. <https://doi.org/10.1371/journal.pone.0281477>
- Hrciarova, J., Kubelkova, K., Bostik, V., Rychlik, I., Karasova, D., Babak, V., Datkova, M., Simackova, K., & Macela, A. (2024). Modulation of gut microbiome and autism symptoms of ASD children supplemented with biological response modifier: A randomized, double-blinded, placebo-controlled pilot study. *Nutrients*, 16(13), 1988. <https://doi.org/10.3390/nu16131988>
- Johnson, C. P., Myers, S. M., & American Academy of Pediatrics Council on Children With Disabilities. (2007). Identification and

- evaluation of children with autism spectrum disorders. *Pediatrics*, 120(5), 1183–1215. <https://doi.org/10.1542/peds.2007-2361>
- Kotagal, S., Malow, B., Spruyt, K., Wang, G., Bolaños Almeida, C. E., Tavera Saldaña, L. M., Blunden, S., Narang, I., Ipsiroglu, O. S., Bruni, O., Strazisar, B. G., Simakajornboon, N., Nunes, M. L., & Cortese, S. (2024). Melatonin use in managing insomnia in children with autism and other neurogenetic disorders - An assessment by the international pediatric sleep association (IPSA). *Sleep Medicine*, 119, 222-228. <https://doi.org/10.1016/j.sleep.2024.04.008>
- Kovacheva, E., Gevezova, M., Maes, M., & Sarafian, V. (2024). Mast cells in autism spectrum disorder—the enigma to be solved? *International Journal of Molecular Sciences*, 25(5), 2651. <https://doi.org/10.3390/ijms25052651>
- Lee, J. D., Terol, A. K., Yoon, C. D., & Meadan, H. (2024). Parent-to-parent support among parents of children with autism: A review of the literature. *Autism*, 28(2), 263-275. <https://doi.org/10.1177/13623613221146444>
- Li, S., May, C., Pang, T. Y., Churilov, L., Hannan, A. J., Johnson, K. A., & Burrows, E. L. (2024). Mice with an autism-associated R451C mutation in *Neuroligin-3* show intact attention orienting but atypical responses to methylphenidate and atomoxetine in the mouse-Posner task. *Psychopharmacology (Berl)*, 241(3), 555–567. <https://doi.org/10.1007/s00213-023-06520-6>
- Lisk, C., Mische Lawson, L., Sugiura, B., Humpherys, D., & Rao, G. (2024). Exploring play interactions of children with autism spectrum disorders and their pets. *OTJR (Thorofare, NJ)*, 44(2), 179-186. <https://doi.org/10.1177/15394492231188311>
- Liu, Q. Q., Mi, J., Du, Y. Y., Rong, Z., Qin, Y., Jiang, W., Li, X., Yu, J. Y., Yang, L., Du, X. Y., Yang, Q., & Guo, Y. Y. (2024). Lotusine ameliorates propionic acid-induced autism spectrum disorder-like behavior in mice by activating D1 dopamine receptor in medial prefrontal cortex. *Phytotherapy Research*, 38(2), 1089-1103. <https://doi.org/10.1002/ptr.8098>
- Liu, Q. Q., Mi, J., Du, Y. Y., Rong, Z., Qin, Y., Jiang, W., Li, X., Yu, J. Y., Yang, L., Du, X. Y., Yang, Q., & Guo, Y. Y. (2024). Lotusine ameliorates propionic acid-induced autism spectrum disorder-like behavior in mice by activating D1 dopamine receptor in medial prefrontal cortex. *Phytotherapy Research*, 38(2), 1089-1103. <https://doi.org/10.1002/ptr.8098>
- Luckett, T., Bundy, A., & Roberts, J. (2007). Do behavioural approaches teach children with autism to play or are they pretending? *Autism*, 11(4), 365–388. <https://doi.org/10.1177/1362361307078135>
- Manning, C. (2024). Visual processing and decision-making in autism and dyslexia: Insights from cross-syndrome approaches. *Quarterly Journal of Experimental Psychology*, 77(10), 1937-1948. <https://doi.org/10.1177/17470218241264627>
- Marra, P. M., Fiorillo, L., Cervino, G., D'Amico, C., Crimi, S., Meto, A., Minervini, G., Ciccù, M. (2024). Dental problems in children with autism: A 5-year study. *Journal of Clinical Pediatric Dentistry*, 48(1), 26–31. <https://doi.org/10.22514/jocpd.2024.004>
- Matson, J. L., & Goldin, R. L. (2014). Diagnosing young children with autism. *International Journal of Developmental Neuroscience*, 39, 44–48. <https://doi.org/10.1016/j.ijdevneu.2014.02.003>
- Meng, J., Han, L., Zheng, N., Wang, T., Xu, H., Jiang, Y., Wang, Z., Liu, Z., Zheng, Q., Zhang, X., Luo, H., Can, D., Lu, J., Xu, H., Zhang, Y. W. (2022). Microglial *Tmem59* deficiency impairs phagocytosis of synapse and leads to autism-like behaviors in mice. *Journal of Neuroscience*, 42(25), 4958–4979. <https://doi.org/10.1523/JNEUROSCI.1644-21.2022>
- Moerkerke, M., Daniels, N., Tibermont, L., Tang, T., Evenepoel, M., Van der Donck, S., Debbaut, E., Prinsen, J., Chubar, V., Claes, S., Vanaudenaerde, B., Willems, L., Steyaert, J., Boets, B., Alaerts, K. (2024). Chronic oxytocin administration stimulates the oxytocinergic system in children with autism. *Nature Communications*, 15(1), 58. <https://doi.org/10.1038/s41467-023-44334-4>
- Myers, S. M., Johnson, C. P., & American Academy of Pediatrics Council on Children With Disabilities. (2007). Management of children with autism spectrum disorders. *Pediatrics*, 120(5), 1162–1182. <https://doi.org/10.1542/peds.2007-2362>

- Pang, R. C. C., Ho, M. S. H., & Wong, P. W. C. (2024). A review of the literature on the multiple forms of stigmatization of caregivers of children with autism among ethnic minority groups. *Journal of Racial and Ethnic Health Disparities*, 11(1), 545-559. <https://doi.org/10.1007/s40615-023-01540-6>
- Reis, S. L., & Monteiro, P. (2024). From synaptic dysfunction to atypical emotional processing in autism. *FEBS Letters*, 598(3), 269-282. <https://doi.org/10.1002/1873-3468.14801>
- Rexrode, L. E., Hartley, J., Showmaker, K. C., Challagundla, L., Vandeweghe, M. W., Martin, B. E., Blair, E., Bollavarapu, R., Antonyraj, R. B., Hilton, K., Gardiner, A., Valeri, J., Gisabella, B., Garrett, M. R., Theoharides, T. C., & Pantazopoulos, H. (2024). Molecular profiling of the hippocampus of children with autism spectrum disorder. *Molecular Psychiatry*, 29(7), 1968-1979. <https://doi.org/10.1038/s41380-024-02441-8>
- Roh, S. H., Mendez-Vazquez, H., Sathler, M. F., Doolittle, M. J., Zaytseva, A., Brown, H., Sainsbury, M., & Kim, S. (2024). Prenatal exposure to valproic acid reduces synaptic δ -catenin levels and disrupts ultrasonic vocalization in neonates. *Neuropharmacology*, 253, 109963. <https://doi.org/10.1016/j.neuropharm.2024.109963>
- Samanta, P., Panigrahi, A., Senapati, L. K., Mishra, D. P., Ravan, J. R., & Mishra, J. (2022). Maladaptive behavior and associated factors among young children with autism. *Indian Journal of Pediatrics*, 89(11), 1134-1136. <https://doi.org/10.1007/s12098-022-04286-x>
- Sharna, S. S., Balasuriya, G. K., Hosie, S., Nithianantharajah, J., Franks, A. E., & Hill-Yardin, E. L. (2020). Altered caecal neuroimmune interactions in the *Neurologin-3* R451C mouse model of autism. *Frontiers in Cellular Neuroscience*, 14, 85. <https://doi.org/10.3389/fncel.2020.00085>
- Shi, X., Lu, C., Corman, A., Nikish, A., Zhou, Y., Platt, R. J., Iossifov, I., Zhang, F., Pan, J. Q., & Sanjana, N. E. (2023). Heterozygous deletion of the autism-associated gene *CHD8* impairs synaptic function through widespread changes in gene expression and chromatin compaction. *American Journal of Human Genetics*, 110(10), 1750-1768. <https://doi.org/10.1016/j.ajhg.2023.09.004>
- Simpson, K., Imms, C., & Keen, D. (2022). The experience of participation: Eliciting the views of children on the autism spectrum. *Disability and Rehabilitation*, 44(9), 1700-1708. <https://doi.org/10.1080/09638288.2021.1903100>
- Ten Hoopen, L. W., de Nijs, P. F., Slappendel, G., van der Ende, J., Bastiaansen, D., Greaves-Lord, K., Hakkaart-van Roijen, L., Hillegers, M. H., & the Dutch Autism Study Group. (2023). Associations between autism traits and family functioning over time in autistic and non-autistic children. *Autism*, 27(7), 2035-2047. <https://doi.org/10.1177/13623613231151784>
- Thomas, M. S., Davis, R., Karmiloff-Smith, A., Knowland, V. C., & Charman, T. (2016). The over-pruning hypothesis of autism. *Developmental Science*, 19(2), 284-305. <https://doi.org/10.1111/desc.12303>
- Truong, D. M., Mire, S. S., Day, S. X., Ni, L., & Keller-Margulis, M. (2023). A cross-cultural comparison of a measure of parent perceptions among families of children with autism in Vietnam. *Autism*, 27(4), 997-1010. <https://doi.org/10.1177/13623613221141262>
- Vakilzadeh, G., Maseko, B. C., Bartely, T. D., McLennan, Y. A., & Martínez-Cerdeño, V. (2024). Increased number of excitatory synapses and decreased number of inhibitory synapses in the prefrontal cortex in autism. *Cerebral Cortex*, 34(13), 121-128. <https://doi.org/10.1093/cercor/bhad268>
- Velmeshev, D., Schirmer, L., Jung, D., Haeussler, M., Perez, Y., Mayer, S., Bhaduri, A., Goyal, N., Rowitch, D. H., & Kriegstein, A. R. (2019). Single-cell genomics identifies cell type-specific molecular changes in autism. *Science*, 364(6441), 685-689. <https://doi.org/10.1126/science.aav8130>
- Wang, L., Mirabella, V. R., Dai, R., Su, X., Xu, R., Jadali, A., Bernabucci, M., Singh, I., Chen, Y., Tian, J., Jiang, P., Kwan, K. Y., Pak, C., Liu, C., Comoletti, D., Hart, R. P., Chen, C., Südhof, T. C., & Pang, Z. P. (2024). Analyses of the autism-associated *neurologin-3* R451C mutation in human neurons reveal a gain-of-function synaptic

- mechanism. *Molecular Psychiatry*, 29(6), 1620-1635. <https://doi.org/10.1038/s41380-022-01834-x>
- Wang, Z. J., Rein, B., Zhong, P., Williams, J., Cao, Q., Yang, F., Zhang, F., Ma, K., & Yan, Z. (2021). Autism risk gene *KMT5B* deficiency in prefrontal cortex induces synaptic dysfunction and social deficits via alterations of DNA repair and gene transcription. *Neuropsychopharmacology*, 46(9), 1617–1626. <https://doi.org/10.1038/s41386-021-01029-y>
- Williams, E., Costall, A., & Reddy, V. (1999). Children with autism experience problems with both objects and people. *Journal of Autism and Developmental Disorders*, 29(5), 367–378. <https://doi.org/10.1023/a:1023026810619>
- Wu, J., Zhang, J., Chen, X., Wettschurack, K., Que, Z., Deming, B. A., Olivero-Acosta, M. I., Cui, N., Eaton, M., Zhao, Y., Li, S. M., Suzuki, M., Chen, I., Xiao, T., Halurkar, M. S., Mandal, P., Yuan, C., Xu, R., Koss, W. A., Du, D., Chen, F., Wu, L. J., & Yang, Y. (2024). Microglial over-pruning of synapses during development in autism-associated *SCN2A*-deficient mice and human cerebral organoids. *Molecular Psychiatry*, 29(8), 2424–2437. <https://doi.org/10.1038/s41380-024-02518-4>
- Xiong, G. J., Cheng, X. T., Sun, T., Xie, Y., Huang, N., Li, S., Lin, M. Y., & Sheng, Z. H. (2021). Defects in syntabulin-mediated synaptic cargo transport associate with autism-like synaptic dysfunction and social behavioral traits. *Molecular Psychiatry*, 26(5), 1472–1490. <https://doi.org/10.1038/s41380-020-0713-9>
- Xu, D., Zhi, Y., Liu, X., Guan, L., Yu, J., Zhang, D., Zhang, W., Wang, Y., Tao, W., & Xu, Z. (2023). *WDR62*-deficiency causes autism-like behaviors independent of microcephaly in mice. *Neuroscience Bulletin*, 39(9), 1333–1347. <https://doi.org/10.1007/s12264-022-00997-5>
- Yoon, N., Kim, S., Oh, M. R., Kim, M., Lee, J. M., & Kim, B. N. (2024). Intrinsic network abnormalities in children with autism spectrum disorder: An independent component analysis. *Brain Imaging and Behavior*, 18(2), 430-443. <https://doi.org/10.1007/s11682-024-00858-x>

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of the publisher and/or the editor(s). This publisher and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

© Copyright (2024): Author(s). The licensee is the journal publisher. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:

<https://www.sdiarticle5.com/review-history/126641>