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The Neurobiological Basis for Social Affiliation in Autism Spectrum Disorder and Schizophrenia

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Abstract

Social interaction and communication are complex behavioral paradigms involving many components. Many different neurotransmitters, hormones, sensory inputs, and brain regions are involved in the act of social engagement and verbal or nonverbal communication. Autism Spectrum Disorder (ASD) and schizophrenia are two neurodevelopmental disorders that have social and language deficits as hallmark symptoms, but show very different etiologies. The output of social dysfunction is common to both ASD and schizophrenia, but this likely arises from very different pathophysiological means. This review will attempt to compile and interpret human and animal studies showing the neurobiological basis for the development of social and language deficits in ASD and schizophrenia as well as a comparison of the two disorders.

Keywords

schizophrenia; autism spectrum disorder; social deficits; social affiliation; language deficits; neurodevelopmental disorders

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder consisting of many subsets along a spectrum of severity. Individuals with ASD present with an array of symptoms that includes social deficits, obsessive tendencies, self-injurious behavior, aggression, anxiety, depression, learning deficits, memory deficits, and language deficits. ASD is typically diagnosed in early childhood, but can be predicted as early as infancy. ASD is thought to be gender specific, occurring 5 times more often in boys than girls. This review will focus on the widely accepted symptoms of ASD, those that have been characterized largely by male individuals presenting with the disorder. There are thoughts that fewer females are diagnosed with ASD because their symptoms may present differently

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

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than males, though this review will only briefly touch on that discussion and what is currently known about differences between males and females with ASD.

Social deficits are a hallmark of ASD with many of its symptoms directly and indirectly contributing to social isolation. Individuals with ASD often present with language and communication difficulties [1]. Difficulties in communication and language learning can directly result in decreased social interaction from a very early developmental stage. Face processing and body language reading are also impaired in individuals with ASD, making social interaction more difficult. Studies have shown that face processing is impaired as early as infancy in individuals who develop ASD later in childhood [2]. Difficulty with facial processing can predict problems with facial recognition [3] and language deficits [4] later in life. Anxiety and depression can also contribute to social isolation, making interaction with others more difficult through increased social anxiety and decreased motivation to socialize, respectively. Studies have shown that higher levels of self-reported anxiety correlates with increased loneliness in adolescents with ASD [5]. The above study also shows increased depression and social disability correlated with child withdrawal as reported by caregivers of individuals with ASD [5].

The word “schizophrenia” comes from two Greek words for “to split” and “mind” [6]. This refers to the splitting of mental functions that patients present with, not the splitting of personalities [6]. Though asociality and social dysfunction can be a major component [7], schizophrenia is not defined as a social disorder, but rather social dysfunction and isolation are considered a functional consequence of the disorder [7]. However, recent changes in the view of schizophrenia note that social isolation can be a major part of the pathophysiology of the disorder [8]. This alteration in thinking surrounding schizophrenia may yield new insights into symptoms and treatments of the disorder.

Unlike ASD, schizophrenia is typically diagnosed later in life. Individuals often present with schizophrenia in early adulthood, from 20–30 years of age [7–9], though some individuals present earlier in life with what is known as childhood-onset schizophrenia. Individuals with schizophrenia have many positive, negative, and cognitive symptoms, though the most devastating may be the inability to participate in ordered communication. Positive symptoms include delusions, hallucinations, incoherence or disorganized speech, and disorganized or catatonic behavior [7]. These symptoms can feed forward into social deficits by inhibiting the ability to socialize.

Negative symptoms include decreased self-motivation, deficits in speech, anhedonia, and flat affect [7]. These directly contribute to social disorder in schizophrenia by decreasing motivation for social interaction and altering emotions and social communication. Furthermore, social isolation seems to result in and exacerbate symptoms of schizophrenia in animal models [10–11]. Schizophrenia typically also consists of social or occupational dysfunction, resulting from the disorder’s primary symptoms. Functioning in work and personal relationships as well as self-care can be severely affected. Social communication deficits are significantly affected by negative symptoms of schizophrenia, which results in a reduced capacity as compared to normal individuals [12]. Communication deficits can often alienate individuals from society, hinder professional and personal relationships, reduce

chances of obtaining adequate medical and psychological care, and increase likelihood of homelessness and self-medication. All of these result in a lower quality of life (QOL), which is known to be correlated with severity of symptoms [13].

Significantly reduced nonverbal communication has also been shown to be correlated with severity of symptoms in patients with schizophrenia [14]. Furthermore, individuals with schizophrenia have been shown to have reduced nonverbal synchrony, or imitation, with control interactants [15]. These analyses of nonverbal communication can serve as indicators for symptom severity as well as cognition and communication deficits in patients with schizophrenia. Cognitive symptoms of schizophrenia include decreased executive functioning, attention deficits, and memory deficits [7–8]. These symptoms can contribute to social affiliation deficits through inability to carry on conversation, inability to pay attention to interactants, and inability to recall information needed for everyday personal or professional interactions. These symptoms are particularly troublesome for professional relationships and make leading a normal life difficult.

Schizophrenia and ASD have many commonalities including gender specificity, language and communication deficits, cognitive deficits, and social deficits. Both disorders tend to occur more frequently in males, though ASD gender specificity is significantly more pronounced [6]. Patients with schizophrenia or ASD will typically present with language or other communication deficits that contribute significantly to social impairments [1, 12, 14–15]. Both disorders also consist of social cognitive deficits including facial recognition, recognition of emotion, and social perception along with other cognitive deficits [2–3, 15].

Neurobiological basis for social deficits in ASD

Dr. Leo Kanner originally characterized ASD in 1943 by describing 11 children with high intelligence who seemed to desire aloneness and abhor change in their daily routines [16]. Since then, many studies have been performed in regard to the behavioral and molecular characteristics involved in the pathophysiology of ASD. The symptom of ASD that seems to be the most pronounced and also the most debilitating is social dysfunction. A number of theories, based mainly on genetic mutations [20–21], neurotransmission deficits [22–23], hormones and gender [19], and abnormalities in the immune system [17–18] attempt to explain the underlying mechanism(s) for social deficits in ASD. Indeed, many of the genetic as well as environmental rodent preparations accurately model significant social deficits along with other core symptoms seen in ASD [18, 23–26]

Genetic susceptibility is an accepted component of ASD as approximately 6–25% of individuals with the disorder have a mutation in an ASD candidate gene [18–19]. The most well characterized genetic models of ASD include SH3 and multiple ankyrin repeat domains (SHANK) family mutants, methyl CpG-binding protein 2 (MECP2) mutants, and contactin associated protein-like 2 (CNTNAP2) mutant mice. Each mutant mouse model is based on one or more human genetic studies showing individuals with ASD or ASD-like symptoms have a mutation in the gene of interest that can be linked to physical or behavioral characteristics of the disorder. Below, we will review the literature on social deficits seen in human and rodent studies of these mutations.

The SHANK/ProSAP (SHANK/proline-rich synapse-associated protein) family of proteins includes SHANK1, SHANK2, and SHANK3. These proteins play important role in organizing proteins at the post synaptic density (PSD) of excitatory synapses [27–28] as well as neurotransmitter trafficking and spine integrity [29]. Furthermore, mutations in SHANK family members have been found in ASD subjects [30]. Accumulating data show that mutations in SHANK genes result in ASD-like behaviors including repetitive behaviors, altered communication, and social interaction deficits in rodents [24, 30–34].

Shank3 mutations occur in approximately 0.5% of individuals with ASD [35]. SHANK3 mutant mice were the first genetic model of SHANK mutations [24] and are the most well characterized of the shank mutants. Five different Shank3 mutant mice have been reported [36–38], all but one exhibiting a strong phenotype of social abnormalities among other core symptoms of ASD [39]. Two Shank 1 [40–42] mutants and one Shank 2 mutants [38, 43] have also been developed and characterized. All three of these mutants show abnormal social behavior and ultrasonic vocalization (USV) profile. Male Shank1 mutants showed reduced social sniffing and reduced number of calls in male-female interactions [40–42]. Shank2 mutant mice with exons 6–7 targeted show reduced interaction with a novel mouse in the three-chamber test with no impaired social recognition or olfaction [43]. Shank2 mutants with only exon 7 targeted show normal initiation of social interaction, but decreased ability to continue social contact in the resident-intruder test as well as decreased social interaction in the 3 chamber test. USV profile in these mice shows increased number of calls in female pups and reduced number of calls as well as longer latency of call during adult female-female interaction. Male Shank3 exon 7 mutant mice show no abnormal USV profile [38].

Mutations in MECP2 result in a disorder called Rett Syndrome. 95% of individuals with this disorder have a randomly occurring mutation in the MECP2 gene on the X chromosome. MECP2 is an epigenetic factor that binds to methylated DNA to regulate chromatin structure and gene expression [44–45]. Mutations in this gene can cause alterations in the expression of many other proteins that account for the wide array of symptoms seen in individuals with Rett Syndrome. Symptoms of the disorder include seizures, muscle weakness, repetitive movements, slowed brain and head growth, intellectual disability, loss of language, and Autistic-like symptoms including social interaction deficits and loss of purposeful eye contact [46–47]. This disorder largely affects females because the mutation occurs on the X chromosome, typically causing fetal or infant lethality in males with the disorder. Individuals with Rett syndrome display irreversible loss of social interaction and language learning that occurs from 1–4 years of age. MECP2 mutant mice show similar symptoms to the human disorder in that their symptoms are more pronounced in males than females and the brain size and weight is reduced [25]. The female mice are heterozygous and have mosaic expression of MECP2 in the body, mimicking the clinical pathology. Males are hemizygous and show severe encephalopathy and more pronounced symptoms than the females, but do not show infant lethality [47].

The reelin gene (RELN) has also been implicated in both ASD and schizophrenia is important in proper brain development. Reelin is a large extracellular protein secreted by neurons in superficial areas of the cortex, cerebellum, and hippocampus [48–49]. This

protein is responsible for neuronal migration during development [50–51], but is also expressed in the adult brain [49]. Reelin is located on the long arm of chromosome 7, which is a region of DNA with many ASD susceptibility loci [48]. Many reelin mutations have been implicated in ASD, the most studied of which are: rs736707, rs362691, and alterations in number of GGC repeat variants [52]. One meta-analysis revealed that the rs362691, which is a 22 C/G transversion, was significantly correlated with increased risk for the development of ASD, but GGC repeat variants and the rs736707 mutation were not. Six studies with 640 ASD subjects and 751 controls were used for the meta-analysis of the rs736707 mutation. Seven studies containing 426 ASD cases, 454 controls, and 365 families were used for the rs362691 analysis. Seven studies including 276 ASD subjects, 613 control subjects, and 485 families were used to study the GGC repeat variant of RELN [52]. Another study showed a correlation between GGC repeats and etiology of ASD in 126 multiple-incidence families [53]. This study [53] found no correlation between GGC repeat variants and risk for development of ASD, which mirrors a previous study [52]. Another study showed an association between rs736707 mutation, a single nucleotide polymorphism (SNP) in intron 59 of RELN, and ASD susceptibility [54]. HRM mice, mice that are haploinsufficient for reelin, were developed to study the effects of reduced reelin expression. These mice are typically used for studying reelin in schizophrenia, but some studies have been performed on their social interaction and USV profiles. No alterations in male-female interaction profile or USV profile were observed [55]. Taking the body of literature relating Reelin and ASD, it seems that there is a loose tie between the two with mixed results in some studies.

γ -amino butyric acid (GABA) is the brain's major inhibitory neurotransmitter, and inhibitory neurotransmission abnormalities have been linked to ASD [56–61]. There are two major types of GABA receptors, GABAA and GABAB. GABAA receptors facilitate fast inhibitory neurotransmission in the central nervous system. GABAB receptors differ significantly from GABAA receptors in structure and function. GABAB receptors will not be discussed in this review as they have not been tightly linked with ASD susceptibility. However, two studies have shown that arbaclofen agonism of GABAB receptors reverses social dysfunction in humans [56] and social deficits in rodents [57]. GABAA α 1 subunit is expressed ubiquitously in the brain and is the major receptor in the GABA system. A significant reduction in GABAA α 1 protein levels has been found in the frontal cortex of ASD subjects, but mRNA levels remain unchanged suggesting receptor degradation occurs in ASD [58]. This results in reduced GABA signaling in ASD, accounting for inhibitory neurotransmission deficits in the disorder. Increased polymorphisms in GABAA receptor subunits have also been found in individuals with ASD as compared to controls [59–60]. Animal studies have also been performed to further study GABAA in ASD. Enhancement of GABAA action has been shown to reverse behavioral deficits in a mouse model of ASD [61], while reduction in GABAA signaling exacerbates deficits [61].

Genetic mutations account for a possible 25% of ASD cases, but what about those individuals who have been diagnosed with ASD, but do not carry a known mutation? Are these individuals carrying a mutation in an unidentified candidate gene or is there another root cause for their symptoms? Many would argue that environmental triggers are a major if not determining factor in ASD susceptibility. The brain has many critical periods where

disruption in development can have long-lasting and detrimental effects that result in altered behaviors down the line. These environmental disruptions can occur prenatally, perinatally, or postnatally and can affect many body systems including the brain and immune systems. Many theories for the development of ASD include hormonal changes during development, immune dysfunction, cellular stress, and many others.

Many studies have shown that hormonal alterations are part of ASD pathophysiology. Estrogen has not only been shown to be an effective adjunctive therapy for treatment-resistant schizophrenia [62], but improves ASD-like symptoms in mice [63]. Estrogen receptor β is known to be reduced in individuals with ASD [64] and boosting estrogen receptor beta signaling improves ASD-like symptoms in zebrafish [65].

Oxytocin and vasopressin are known to have social behavior effects due to their action in attachment and communication. Both hormones are implicated in ASD and schizophrenia, though more is known about oxytocin's role in these disorders. It is known that ASD is significantly correlated with decreased oxytocin gene expression [66] and oxytocin levels in plasma [67]. Oxytocin is known as the affiliation hormone and is thought to be involved in social interaction [68–69], maternal behavior [70–71], sexual contact [72], and pair bonding [73]. Oxytocin and vasopressin are reduced in plasma [67]. Furthermore, SNPs in the gene for oxytocin (OXT) as well as the gene for oxytocin receptor (OXTR) have been found in individuals with ASD [74–77]. Many studies have shown that administration of oxytocin intranasally can reverse social behavior deficits seen in the disorder at both early childhood and adult stages of ASD. Yatawara et al 2015 [78] show administration of intranasal oxytocin improved caregiver-related social response in young children. Another study [79] shows that administration of oxytocin increases activity in the striatum, medial prefrontal cortex, and middle frontal gyrus of children with ASD during social judgment. Studies also indicate that administration of intranasal oxytocin improves social eye contact [68] and social communication [80] in adults with ASD.

The immune system can be severely dysregulated in individuals with ASD and it has been shown to be involved in some other symptoms of the disorder. Gastrointestinal dysfunction [81–82], microglial alterations [83–84], and aberrant immune responses [85] have been characterized with ASD. All of these symptoms have an immune component, which is why many animal models have been developed that focus on immune dysfunction in order to study its importance in the disorder. The most widely used immune model for ASD and other neuropsychiatric disorders is the Maternal Immune Activation (MIA) model, also sometimes referred to as the Poly(I:C) model. This model has been used to study schizophrenia and has more recently been applied to ASD and other neuropsychiatric disorders. In the MIA model, a pregnant mouse is injected with Poly(I:C) to trigger a controlled immune response and her pups are studied in order to determine how they are affected by the in utero immune stimulation [86]. Studies have shown that these pups show some ASD-like tendencies including anxiety [87]. Another immune dysfunction in ASD is the involvement of microglial cells in the pathophysiology of the disorder [88]. Microglial cells are the immune cells of the brain and many studies have shown that alterations in microglia have been connected to ASD [89]. Deficiencies in neuron-microglial signaling have been shown to reduce social interaction in rodent models [84]. Another theory for ASD

development that is related to immune and inflammatory response is endoplasmic reticulum (ER) stress. ER stress response (also known as Unfolded Protein Response) is overactive in many disease states including mood disorders [89–91], inflammation [92], neurodegenerative diseases [93–94], and neurodevelopmental disorders [95–96]. ER stress has been recently implicated in the pathophysiology of ASD [95–96]. ER stress can alter the delicate balance of post-translational modifications occurring in the cell, which can lead to the improper production or degradation of functional proteins. ER stress is known to activate NF- κ B and the downstream action of NF- κ B is thought to be responsible for behavioral deficits in ASD. Other inflammatory markers are also elevated in ASD including IL-1 β and IFN- γ [97]

Neurobiological basis for social deficits in schizophrenia

Human and animal studies have revealed that many genetic and environmental factors may lead to increased susceptibility for the development of schizophrenia. There are many genes implicated in schizophrenia, but the ones covered in this review are limited to those that are also implicated in social deficits and ASD pathophysiology. These factors include genetic and neurotransmitter dysfunction including mutations in reelin gene, SHANK family mutations, and GABA/glutamate dysregulation. Some environmental factors that have been implicated in schizophrenia pathophysiology include: maternal immune activation, oxidative stress, and prenatal hypoxia.

Similar copy number variants (CNVs) have been found in many genes that are implicated in both ASD and schizophrenia [98–101]. Interestingly, different mutations in the same SHANK gene can result in schizophrenia phenotype instead of ASD-like phenotype [102]. A nonsense mutation in SHANK3 that results in the replacement of an arginine (R1117X) with a stop codon has been identified in individuals who developed schizophrenia, but had no developmental ASD or autistic features [103]. A recent study has compared two mutant mouse lines, one line was created based on a mutation found in humans with ASD (InsG3680 mutation) and the other (R1117X mutation) was created based on the mutation that resulted in patient development of schizophrenia [103]. Both lines exhibited postsynaptic signaling complex defects, social behavior deficits, and anxiety-like behavior. The R1117X mutant showed synaptic defects in the prefrontal cortex (PFC), while the InsG3680 mutants did not. It is still not fully clear how two different mutations in the same gene that result in significantly reduced or no expression of SHANK3, but exhibit different neurological phenotypes. The above study suggests that the different alleles of SHANK3 may result in alterations at different developmental stages or result in different levels of mRNA stability, resulting in varying neurobehavioral outcomes.

MECP2 is another gene that is implicated in both ASD and schizophrenia. MECP2 is a transcriptional activator and repressor, so it can affect the expression of many genes [104]. MECP2 is known to be involved in aggression and social behavior [104]. De Novo mutations [105], missense mutations [105], and 3' UTR variants [106] in MECP2 have been identified in individuals with ASD and schizophrenia.

Reelin is involved in the structure and function of cortex and hippocampus as well as the maintenance and plasticity of many brain networks [107]. Genetic variations in the reelin gene (RELN) have been found to be associated with schizophrenia [108–109]. Reduced reelin protein expression, approximately 50% of control levels, has also been found in the prefrontal cortex of individuals with schizophrenia [110–113]. Heterozygous reeler mice (HRM) are haploinsufficient for RELN and were developed to study the effects of significantly reduced expression of reelin. These mice show many symptoms similar to patients with schizophrenia including social deficits [114]. Another mouse model of reduced reelin expression in brain using methionine treatment also showed impaired social recognition memory [115] suggesting a potential role of reelin in social behavior.

Dysfunctional neurotransmitter trafficking is another known problem in schizophrenia, though its root cause has yet to be elucidated. Both reelin and Shank family member proteins are involved in trafficking of neurotransmitters [116] and synaptic scaffolding and integrity [117], but they are likely not the only factors affecting neurotransmitters like GABA, glutamate and dopamine. GABA dysfunction is implicated in ASD as well as schizophrenia and is thought to be responsible for inhibitory transmission and social deficits in ASD [118] as well as verbal working memory and flat affect [119] in schizophrenia. Reduced GABAA receptor [120] and related protein [121] expression has been found in cortex of individuals with schizophrenia. One study shows that disrupting proper GABAA α 2 clustering in frontal cortex in mice induces working memory and PPI deficits [120], which mimics human pathophysiology and symptomatology.

Oxytocin and vasopressin are implicated in ASD, schizophrenia, and other neuropsychiatric conditions [121]. Reduced oxytocin and vasopressin have been observed in plasma [122] and cerebrospinal fluid (CSF) of schizophrenic individuals. Oxytocin has antipsychotic effects [123] and a significant role in social functioning [124–127]. Reduced plasma oxytocin has been linked to social skill deficit, recognition of emotion, and social cue recognition in schizophrenia [124–125]. Intranasal oxytocin administration has shown to improve social cognition and social skills in individuals with schizophrenia [126–127]. It is important to note that many studies have found no significant differences in oxytocin plasma [128] and CSF [129–130] levels in schizophrenia as compared to healthy controls. Some studies have also found conflicting results in increased oxytocin and levels in CSF [131]. Genetics studies of OXT and OXTR in schizophrenia are limited, but some genetic variants of OXT have been discovered [132]. SNPs in OXTR have also been found to be associated with schizophrenia [133]. Some genetic variants of OXT and OXTR have been associated with treatment response [132] and loosely correlated with negative symptom severity [132]. Similar to plasma and CSF studies relating to oxytocin in schizophrenia, genetic studies have been inconsistent [133–134]. Together, these studies suggest that the role of oxytocin in schizophrenia is not well defined and other factors may be at play in social interaction in schizophrenia.

In addition to candidate genes, environmental or other factors are also thought to contribute to the development of schizophrenia. Gestational events have been implicated in many neurological disorders and schizophrenia is thought to be one of those. Prenatal hypoxia [135–137] and maternal infection [138–141] are significantly correlated with the

development of schizophrenia later in life. The general consensus of environmental factors is the “two hit” hypothesis which concludes that genetic (family history) and environmental factors combine to produce a significantly increased risk of psychosis development [142–144].

Future Directions

Both ASD and schizophrenia are clinically heterogeneous disorders with patients suffering from varying severities or sets of symptoms. These disorders remain elusive in terms of pathophysiology, though some genetic mutations, environmental factors, and other correlations between ASD and schizophrenia have been found. Molecular mechanisms behind symptoms are largely unknown despite the large amount of literature on both disorders. It seems that these disorders stem from a combination of genetic and environmental triggers, some of which are common to both.

The idea that ASD and schizophrenia share risk factors and similar symptomatology is not novel (Figure 1). Many studies have shown molecular and behavioral similarities between the two disorders and more of these studies are published as we learn more about them (Table 1). Different mutations in the same genes can result in the development of both disorders [102], providing a striking example of the similarity of ASD and schizophrenia. Both disorders are generally thought of as genetic disorders as many mutations in genes have been correlated with disease development. Though much work has been done to identify and characterize these mutations, candidate genes have not proven helpful for the development of treatments for either disorder. Many genetic alterations have been shown to be common between both disorders, but these are not the only factors affecting disease development. Genetic mutations are not the major contributor to ASD and schizophrenia development. Despite the myriad of ASD candidate genes, approximately 75% of ASD cases occur without any known genetic mutation in a candidate gene [145].

A more attractive treatment option seems to be targeting environmental or other factors involved in the development of ASD and schizophrenia. The hormonal component of both disorders is striking. Some treatments are already showing promising results in mice and humans. Oxytocin, vasopressin, and estrogen seem to be viable candidates for treatment for both ASD and schizophrenia. Admittedly, this route of treatment does have the potential for significant side effects due to the widespread role of hormones in the body. This target becomes viable when specific action of these hormones is elucidated and targeted therapies can be developed that manipulate specific downstream effects of each hormone. More work needs to be done to specifically elucidate the effects of these hormones on downstream molecules and determine a more specific treatment for individuals with ASD and schizophrenia.

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Figure 1.
Symptoms of ASD, Schizophrenia, and symptoms common to both disorders.

Table 1

Pathophysiological hallmarks shared by both ASD and Schizophrenia: rodent models.

Human Pathophysiology	Rodent Model	Characteristics	References (ASD)	References (Sz)
GABA deficits	Manipulation of GABAA and GABAB	• Arbaclofen agonism of GABAB receptors reverses social dysfunction in humans [56] and rodents [57].	56, 57, 61	113, 114, 115, 144
		• Enhancement of GABAA signaling reverses ASD-like behavioral deficits in rodents and reduction of GABAA signaling exacerbates the symptoms [61]		
		• Disrupted GABAA clustering induces PPI and working memory deficits [144]		
Immune Dysfunction	Maternal Immune Activation model (MIA)	• ASD-like symptoms including anxiety [82]	82	134, 135, 136, 142, 143
		• Schizophrenia-like symptoms including PPI deficits [142, 143]		
MECP2 mutations and reduced expression	Mosaic, reduced MECP2 expression	• Infant lethality and severe encephalopathy in males[25, 47]	25, 47	98, 99, 100
		• Female mice have mosaic expression of MECP2 [25]		
		• Social interaction deficits		
		• Reduced brain size and weight		
Oxytocin and oxytocin receptor deficits	Reduced oxytocin and oxytocin receptor	• Reduced social interaction	62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75	116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129
		• Reduced Reelin expression [55, 108, 109]		
Genetic variations in RELN and reduced reelin protein expression in cortex	HRM	• Reduced Oxytocin in cortex [109]	55, 108, 109	108, 109
		• No altered male-female interaction or USV profile, but altered stress response [55]		
		• Reduced social interaction [108, 109]		
		• Synaptic deficits [96]		
SHANK3 mutations	SHANK3 R1117X Mutant	• Postsynaptic signaling complex abnormalities [96]	39	96, 97, 98
		• Anxiety [96]		
		• Social behavior deficits [39]		
		• PFC synaptic deficits [96]		
		• Schizophrenia-like symptoms [97]		

Human Pathophysiology	Rodent Model	Characteristics	References (ASD)	References (Sz)
	SHANK3 InsG3680 Mutant	<ul style="list-style-type: none">• Postsynaptic signaling complex abnormalities [96]• Anxiety [96]• Social behavior deficits and other ASD-like behavior [96]	96, 97	-

GABA = γ aminobutyric acid; GABAB = GABA receptor B; GABAA = GABA receptor A; MECP2 = Methyl CpG-binding protein 2; RELN = Reelin; HRM = heterozygous reeler mouse; SHANK3 =SH3 and multiple ankyrin repeat domains 3; ASD = Autism Spectrum Disorder; Sz = Schizophrenia