# Influencing factors and intervention therapy of the Autism Spectrum Disorder (ASD)

Ruwei Huang [1, *]

[1] The Affiliated High School of Fujian Normal University, Fujian, China

* Corresponding Author Email: 2021000611@poers.edu.pl

**Abstract.** Autism spectrum disorder (ASD) is a kind of the disorder which is characterized by continuous social interaction and communication disorders, narrow interests and repetitive stereotyped behaviors are the main core symptoms of neurodevelopmental disorders. At the same time, the incidence of the disease increases rapidly and is extremely harmful, which brings huge economic burden to families and society. Therefore, early identification and early intervention are urgently needed. At present, the pathogenesis of ASD is not clear, and there is no perfect diagnostic tools and methods. So far, scholars are still exploring the etiology and pathogenesis of ASD. In the past, researchers have paid attention to the study of twins and found that the prevalence of monozygotic twins is higher than that of dizygotic twins, so as to try to explain the ASD from a genetic perspective.Academic circles generally believe that ASD is caused by the joint action of genetics and environment. In order to find the objective indicators of early recognition of ASD individuals, researchers have actively carried out research on ASD infants, such as twins, the overall processing of isolated faces,event-related potentials (ERP) and other monitoring methods. Traditional ASD psychotherapy mostly focuses on behavioral rehabilitation training, supplemented by some drug treatment.Advanced spatial information technology has certain advantages and potentials for the treatment of autism spectrum disorders.However, at present, the research in this field is relatively scattered and cannot be popularized.

**Keywords:** Autism Spectrum Disorder, Genetic Factors, Environmental Factors, Intervention therapy.

## 1. Introduction

Autism Spectrum disorder (ASD) it is known as a distinct disease with damaged neural development. The main manifestations of patients are serious impairment of the social interaction and communication skills, also the repetitive and the stereotyped interests, behaviors or actions,which will affect their social communication ability and they will behave restrictively and repetitively. Social disorder has always been the core symptom of ASD, which is often accompanied by emotional disorder.In most cases,ASD was diagnosed by age 3 and show symptoms of lack of response to his or her name and avoiding eye contact [1]. Epidemiological studies show that SAD affects 1% to 2% of American children. Previous meta-analysis results of Chinese scholars showed that the incidence of ASD in Chinese children was about 2.4%, and showed a gradual upward trend.In 2020, Centers for Disease Control and Prevention (CDC) has showed that the current incidence rate of autism has risen to 1/54, exceeding the sum of the world's three major diseases (AIDS, cancer, diabetes) [2].

So far, scholars are still exploring the etiology and pathogenesis of ASD. In the past, researchers have paid attention to the study of twins and found that the prevalence of monozygotic twins is higher than that of dizygotic twins, so as to try to explain the ASD from a genetic perspective.In fact, heredity cannot completely explain the pathogenesis of ASD. The comorbidity rate of identical twins does not reach 100%, which means that heredity or other non-Genetic Factors jointly affect the emergence of ASD.At present, the most studied non genetic factors are environmental factors, such as age, society, culture, etc.

Behavioral intervention and drug treatment are the main intervention methods for the ASD, At the same time, cooperate with physical therapy and dietotherapy.However,there is no approved drug for ASD[3].Some clinical treatments cannot completely determine the effectiveness of targeting the core indication of the ASD, and the large sample trials are still not enough.

The purpose of this paper is to provide more insights for the diagnosis and treatment of ASD from the perspective of the pathogenic factors and intervention measures of ASD, combined with the evidence-based evidence in recent years.

## 2. Influencing factors of the ASD

### 2.1. Genetic Factors

It was initially understood that autism spectrum disorders are related to heredity because studies have found that about 10% - 25% of ASD patients are accompanied by potential genetic defects, such as fragile X-chromosome syndrome, nodular sclerosis and Rett syndrome, and also found that harmful mutations have occurred in several disease-related candidate genes in patients, such as genes encoding neural junction proteins, axon proteins and shanks, This also shows that synapses play an important role in the pathogenesis of ASD.

The study on the prevalence rate of families and twins with ASD found that the probability of identical twins suffering from the disease at the same time is 70% - 90%, and the probability of children in the affected families is significantly higher than that in ordinary families, indicating that ASD has high heritability.It can be observed that e familial clustering in families with existing cases of ASD. Younger siblings, especially younger male siblings, have a higher risk for ASD among family members[4].The incidence of ASD in boys is four or more than that in girls.However, except for the sex differences in ASD, there is no other supportive evidence linking it to the X chromosome. Many linkage regions have been reported in some genome-wide linkage studies, but unfortunately none has been replicated in more than two studies. According to the data, there are over 2000 genes, 4500 CNVs (copy number variations) that associated with the ASD [5].

CNVs are closely related to ASD, indicating that the abnormal copy number or expression level of some genes are involved in the pathogenesis of ASD. Gene copy number variation itself may be a risk factor for ASD. The study of yeast shows that the copy number sensitive genes mainly encode structural proteins and regulatory proteins, which need precise matching and interaction. The excess or deficiency of an element in the complex may damage the assembly of the complex and then affect its biological function. For example, synaptic skeleton protein shank is particularly sensitive to dose because it participates in specific protein-protein interactions.

In a clinical study, parents of the Swedish 9-year-old twins were interviewed through telephone to screen children for the psychiatric disorders, including the ASD.Data came from the population-based health registries, and the researchers examined eight psychiatric disorders that known to the co-exist with the autism spectrum disorder. The final study results showed that there were 272 ASD-positive patients, and the prevalence is 1.4%,the ratio of the male to female is 3.5:1. More than half of the people with ASD (50.3%) have four or more coexisting diseases, and only 4% have no other accompanying diseases.When other conditions were added, the rate of the recurrence rose up to 89% in boys and 62.5% in the girls in MZ siblings, on the other hand,the corresponding figures were 44% and 30% in DZ-SS (same-sex) twins. The incidence of ASD recurrence in MZ siblings was 39% (boy 46% and girls 25%). Among MZ twins with ASD dissonance, 32% had no disorder, while 68% had one disorder and 52% had two or more disorders -- the most common being attention deficit hyperactivity disorder (ADHD) and learning disability (LD). For the 64% of the DZ ASD-discordant twins,no disorder was reported[6].

### 2.2. Environmental Factors

Recent evidence shows that the influence of environmental factors on the causes of autism is routinely underestimated. Compared with genetic factors, environmental factors are more improvable, so they can better guide the direction of environmental genetic two-way interaction.Parental age, maternal nutritional and metabolic status, infection during pregnancy, prenatal stress, and exposure to certain toxins, heavy metals, or drugs are all non-genetic factors that related to ASD. Some research shows that paternal age can contribute to the genetic mutation[5].However, other research rejects this

hypothesis. A critical component for brain development is maternal nutritional status throughout pregnancy period. Some micro-nutrient, such as zinc, iron, and vitamin D, will affect the development of neural system. Another factor is maternal infection[7]. Some hypotheses propose that maternal cytokines may shift to the placenta, leading to the gene dysregulation. Maternal medicinal use during pregnancy, particularly those used to treat depression, is correlated with the risk of ASD.

Taking medicine during pregnancy has always been a sensitive topic.Using the valproate during the pregnancy can also cause neurodevelopmental alterations in offspring, including ASD, but the results show that it is dose related[8].

Additionally, other environmental factors may increase the risk of comorbidities such as gastrointestinal disorders, epilepsy and obesity.Gastrointestinal problems are also common in ASD children. Gastrointestinal problems have great impact on ASD children.The disease also has a certain reaction. Gastrointestinal inflammation or allergy problems will cause pathological changes in physiological functions, so that some short peptide fragments that affect the function of the central nervous system can be absorbed into the blood through the digestive tract, and cross the blood-brain barrier to affect the function of the central nervous system, thereby aggravating the symptoms of autism

Researchers also used the genetic informative designs to investigate other biological causes or traits of autism spectrum disorder.The researchers used the medical records and the parental responses from 194 sets of the twins, at least one of which had an autism spectrum disorder.The result finally shows that the maternal age, the age of the paternas, the drugs, the uterine bleeding and the age of gestational do not increase the risk of concussion for ASD in twins.Respiratory distress, juandice, the need for the oxygen after the birth, and the hypoxic marker presence were more easier to appear in the twin people with ASD than people without the ASD[9].

The non-genetic factors discussed in many studies reveal the correlation between risk factors and the onset of autism, not causality. The research results are subject to the influence of accidental conditions, and the accuracy needs to be further explored. Even if the risk rating is more accurate, it cannot be easily relaxed because some factors are still controversial or have been falsified. The low risk rating of autism does not mean that other potential risks can also be excluded. Therefore, it is still necessary to be alert to suspected risks, identify controllable components and regulate them.

## 3. Early identification of ASD

Event related potential (ERP) provides an objective method to study the cortical potential in the process of information processing. It is a real-time non-invasive electrical activity extracted from EEG data. These advantages make ERP technology possible to become a tool to objectively measure the electrophysiological characteristics of human nerves, and to discover potential information processing mechanisms.

Due to its high time resolution, relatively easy to master experimental technology, relatively low research costs,flexible experimental paradigm and other characteristics, it has been greatly developed.In the past 20 years, ERP Research on ASD has increased rapidly.

Patients with ASD have little capacity to recognize their facial emotions through multiple expressions, facial recognition and discrimination. Consequently, the facial treatment mechanism of patients with ASD must be different from that of normal persons.The treatment of facial stimulation was reflected by conspicuous P1 and N170 ERP components.In most studies, the completion, accuracy and response time of experimental related tasks of autistic children can be normal, while the corresponding components of ERP are different from those of the control group.This means that compared with behavioral measurement ERP detection indicators are more sensitive to the changes of sensory processing and advanced cognitive function of cerebral cortex, so ERP technology has a wide application prospect in the fields of screening, early recognition and early diagnosis of children with autis [10].

# 4. The treatment of ASD

## 4.1. Behavioral therapy

Whether ASD has been diagnosed or suspected, it should be treated as soon as possible. Of course, the treatment is also inseparable from the support of the family, and it is also important to train family members.

One of the most popular ways is Applied Behavior Analysis (ABA), which is the initial technique. The fundamental idea behind this approach is to teach the specific abilities in small, organized chunks. Discrete Trail Training (DTT), Early Intensive Behavioral Interventions (EIBI), Pivotal Response Training (PRT), and Verbal Behavioral Intervention are a few examples of ABA kinds. Children between the ages of three and five can use DTT, which is carried out in classrooms. This method uses five distinct trails to teach and simplify instructions: cue, prompt, response, consequences, and inter-trail intervals. EIBI is typically used to detect children under the age of three. VBI focuses on speech and language[11].

PRT focuses on "key" behaviors, which are related to motivation, feedback in response to multiple clues, active initiation, self-management, and empathy. PRT was initially used for active language training of autistic children. In the 21st century, researchers have found that PRT is not only applicable to language teaching, but also to other fields, such as social interaction, common attention, cognition, etc. Later, PRT received more and more scientific demonstrations, and was rated as one of the most scientifically empirical methods in autism intervention by the American scientific community and relevant government departments. Its de effectiveness is beyond doubt.The purpose of this method is the to develop the vocational social and the living skills and teaches these skills in different settings. The activities and predictably organized and related to visual prompts.

Developmental models tend to teach skills that are important to children's development.In the Denver model, therapists focus on areas of deficit,especially levels of mimicking, the understanding and the sharing emotions, the theory of mind, and the social perception. This method still follows the normal developmental sequence. DIR focuses on meeting a child's level of development, not defects. Motion planning and sequencing, sensory processing and modulation can be used to indicate different sensory and motion profiles. It can take advantage of the emotional, social and cognitive abilities of the children by building relationships and environments. RDI focuses on promoting interactive behaviors and active participation in social relationships that can inspire children to learn social skills and gain social relationships[13].

There are still some approaches that are unproven, such as music therapy and animal-based therapy. For example, Dolphin-assisted Therapy (DAT) has become more and more popular since the 1960s.Some studies suggest that dolphins can help humans better communicate with others, but the evidence-based evidence is not perfect, and its effectiveness is threatened.There is no convincing evidence that this method has positive effect to the treatment[14].

## 4.2. Pharmacological interventions

The most commonly prescribed medications for the ASD invalids are Risperdal and Abilify (aripiprazole) (risperidone). Even though the FDA has allowd the drugs to be used for the ASD, they are still not particular treatment. It is an atypical antipsychotic, aripiprazole. Secretory hormone, vitamin B6, and magnesium are all helpful for ASD[12].

Patients with ASD may also experience additional comorbid conditions, such as sleep issues, depression and the bipolar illnesses. Valproic acid can also be used to treat bipolar illness and mood swings in patients with ASD. Additionally, seizures can be treated using dimethylglycine. Heavy hazardous metals can be removed using the 2,3-dimercaptosuccinic acid (DMSA) ,as well as the 2,3-dimercaptopropane-1-sulfonate (DMPS). Immunoglobulins given intravenously can control an immunological response. Therapy with hyperbaric oxygen can reduce the inflammation. The outcome is still not obvious[15].

Researchers are currently developing several experimental therapies. One of the therapies is the use of ampakines, which is a kind of positibe mosulators of synaptic AMPA-type glutamate receptors. Among many other physiological functions, IGF-1 can decline inflammatory responses because if can regulate the cytokine level and synaptic functions. It is proven that IGF-1 has positive effect on treating ASD. Trofinetide (NNZ-2566) is a piece of protein that can produce by IGF-1 metabolism in the brain. Another RAS-MAPK mosulator is Amo-01, which is proven to resue neuronal phenotypes in several knockout mouse models of intellectual disability. Thus, IGF-1 may be a feasible tactic for ASD future treatment[12.16].

### 4.3. Repetitive transcranial magnetic stimulation (rTMS)

Transcranial magnetic stimulation technology is the modern neuro electromagnetic intervention technology. Its principle originates from Faraday's law of electromagnetic induction, that is, through the electromagnetic coil set outside the body to form a vertical magnetic pulse, which then penetrates the scalp, skull and cobweb, and directly affects and acts on the electrical activities of nerve cells in the brain. By using rTMS, low-frequency magnetic pulses can be formed continuously for a long time, which can directly act on the target brain region, resulting in a sustained and non-invasive intervention effect. Because the scientific use of this technology is safe and non-invasive, this technology has been widely used in the treatment and intervention of mental diseases, including autism and depression.

There have been reported results from roughly two placebo double-blind randomized controlled trials (RCTS). The first demonstrates that, when compared to sham rTMS, two weeks of the daily high-frequency rTMS to the bilateral dorsomedial prefrontal cortex can more effectively reduce the symptoms of social interaction in individuals with ASD (n=28). Another study (n=40) shown that high-frequency bilateral DLPFC stimulation for 4 weeks could not enhance the executive performance in the adolescents ASD and young adults ASD. However, there was some studies proof that rTMS had a positive effect on people who had lower baseline adaptive functioning. However, the study's sample size is modest, and there are certain restrictions[17].

## 5. Conclusions

So far, there has not been a clear explanation of the pathogenesis of ASD, and the medical diagnosis of ASD still mainly relies on superficial observation and some limited detection methods. ERP can reflect the neurological abnormalities of the children with the ASD in terms of latency and the amplitude of attention, cognition, face and emotion recognition, executive function and other indicators. It is expected to become a promising biomarker for the detection of ASD. Therefore, we should continue to increase the research on ERP mechanism of ASD children, so as to promote the development of this field.

More researchers are taking part in pertinent studies as a result of the complex pathophysiology and rising frequency of ASDs. It is anticipated that when research is conducted in greater depth, clinical classification and knowledge of ASDs will become clearer, enabling early detection and screening of ASDs. It is essential to develop tailored treatment plans and implement suitable treatment strategies for various patients because the etiology of ASDs varies and is complex for each individual. New therapies are being developed as more and more disease mechanisms are understood. These therapies offer a solid foundation for the tailored treatment of people with ASD, allowing them to enjoy social interaction and lead normal lives.

## References

[1] Sauer AK, Stanton JE, Hans S, et al. Autism Spectrum Disorders: Etiology and Pathology. In: Grabrucker AM, editor. Autism Spectrum Disorders [Internet]. Brisbane (AU): Exon Publications; 2021 Aug 20. Chapter 1.

[2] Genovese A, Butler MG. Clinical Assessment, Genetics, and Treatment Approaches in Autism Spectrum Disorder (ASD). Int J Mol Sci. 2020 Jul 2;21(13):4726.

[3] Baribeau D, Vorstman J, Anagnostou E. Novel treatments in autism spectrum disorder. Curr Opin Psychiatry. 2022 Mar 1;35(2):101-110.

[4] Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L, et al. Recurrence risk for autism spectrum disorders: A baby siblings research consortium study. Pediatrics. 2011;128(3):e488–95.

[5] Wu S, Wu F, Ding Y, Hou J, Bi J, Zhang Z. Advanced parental age and autism risk in children: a systematic review and meta-analysis. Acta Psychiatr Scand. 2017;135(1):29–41.

[6] Sebastian Lundstrom, Abraham Reifenberg, Jonas Melke, Maria Rastam, Nora Kerekes, Paul Lichtenstein, Christopher Gillberg, &Henrik Anckarsater. Autism spectrum disorders and coexisting disorders in a nationwide Swedish twin study. Journal of Child Psychology and Psychiatry 56:6 (2015), pp 702-710.

[7] Careaga M, Murai T, Bauman MD. Maternal Immune Activation and Autism Spectrum Disorder: From Rodents to Nonhuman and Human Primates. Biol Psychiatry. 2017;81(5):391–401.

[8] Modabbernia A, Velthorst E, Reichenberg A. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. Mol Autism. 2017;8(1):1–16.

[9] Froehlich-Santino, W., Londono Tobon, A., Cleveland, S., Torres, A., Phillips, J., Cohen, B., Torigoe, T., Miller, J., Fedele, A., Collins, J., Smith, K., Lotspeich, L., Croen, L. A., Ozonoff, S., Lajonchere, C., Grether, J. K., O'Hara, R., & Hallmayer, J. (2014). Prenatal and perinatal risk factors in a twin study of autism spectrum disorders. Journal of psychiatric research, 54, 100–108.\

[10] Hao Huirui,CuiXioabing,Dong Xainwen. Progress in the application of event-related potentials in autism spectrum disorders [J]. Modern medicine and health,2022,38(2):244-249.

[11] Ackley M, Subramanian JW, Moore JW, Litten S, Lundy MP, Bishop SK. A review of language development protocols for individuals with autism. J Behav Educ. 2019;28(3):362–88.

[12] Lordan R, Storni C, De Benedictis CA. Autism Spectrum Disorders: Diagnosis and Treatment. In: Grabrucker AM, editor. Autism Spectrum Disorders [Internet]. Brisbane (AU): Exon Publications; 2021 Aug 20. Chapter 2.

[13] Mdavarapu S, Marella L, Sangem A, et al. (January 16, 2019) Where is the Evidence? A Narrative Literature Review of the Treatment Modalities for Autism Spectrum Disorders. Cureus 11(1): e3901.

[14] Medavarapu S, Marella LL, Sangem A, Kairam R. Where is the evidence? A narrative literature review of the treatment modalities for autism spectrum disorders. Cureus. 2019;11(1).

[15] Sanchack K, Thomas CA. Autism spectrum disorder: Primary care principles. Am Fam Physician. 2016;94(12):972–9.

[16] Delorme R, Ey E, Toro R, Leboyer M, Gillberg C, Bourgeron T. Progress toward treatments for synaptic defects in autism. Nat Med. 2013;19(6):685–94.

[17] Enticott PG, Barlow K, Guastella AJ, et al. Repetitive transcranial magnetic stimulation (rTMS) in autism spectrum disorder: protocol for a multicentre randomised controlled clinical trial. BMJ Open. 2021 Jul 7;11(7):e046830.