Chapter

Neural Structure and Function in Autism Spectrum Disorder

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Abstract

Autism spectrum disorder (ASD) refers to a group of neurodevelopmental disorders characterized by changes in communication, social interaction, and repetitive behavior, recognized as a public health problem with a sharp increase in its prevalence in the world population. It is known that brain functioning in individuals with ASD presents important deficits. It is essential to understand these deficits to identify and promote new management strategies for the development of this population with ASD. In this sense, the objective of this chapter is to present, through a literature review, the main risk factors that make up ASD, by showing classic and current findings based on neurophysiological changes and treatments.

Keywords: autism spectrum disorder, neurophysiology, neuropathology, polymorphism, learning disabilities

1. Introduction

Autism spectrum disorder (ASD) is a set of heterogeneous conditions of neurological development and encompasses a series of invasive disorders, characterized by the early onset of social communication deficits and restricted and repetitive patterns of sensorimotor behaviors, interests, or activities, associated with important genetic and environmental factors [1].

The prevalence of ASD has increased globally, with the number of diagnoses of children with ASD tripling in the last three decades [2]. In this sense, recent studies by the Centers for Disease Control and Prevention in the United States have shown a prevalence of the disorder in 1 out of every 59 born children [3].

ASD is often comorbid with other disorders such as anxiety, attention-deficit/hyperactivity disorder, and intellectual disability, and some affected individuals also suffer from gastrointestinal, immune, and sleep disorders, suggestive of systemic dysregulation [4].

Autism severity levels may vary widely, with some cases presenting only mild deficits in social interactions, while other cases exhibit severe deficits in social behaviors [5]. These symptoms are present from childhood to adulthood [6].

Although there is a lot of research on the etiology of ASD, this disorder is still a challenge, being considered a multifactorial impairment, with the influence of genetics, epigenetics and environmental factors in its genesis [7, 8]. Individually or in a combination of the factors mentioned above, these disturbances can alter the function of genes and neural tissue in ASD [9].

Recent research on ASD has gained prominence in the scientific community with regard to neurophysiology. Trying to understand the factors that can trigger this disability is of fundamental importance for advancing the comprehension of such a disorder. Therefore, it is of paramount importance not only for the knowledge of traditional ASD concepts, but also for the study of new concepts that previously could not be achieved [10], the study of neurophysiology, which is the science that addresses neuronal physiology and the factors involved that alter synapses, such as genetic, epigenetic, and environmental ones.

Advances in this area of science have been a major challenge for researchers around the world, as the prevalence of ASD has been increasing every year. However, the evolution of neurophysiology in terms of neurogenetics, neuropathology, animal studies, neuroanatomy, and psychophysics has now allowed the clinical staff new tools for the diagnosis and treatment of ASD, such as gene therapies, transcranial electrical stimulation, and cannabis/cannabidiol [11].

2. Genetic and environmental contributors

The etiology of autism is heterogeneous. In the scientific literature, there is convincing evidence that the disorder is influenced by environmental and genetic factors in its pathogenesis; however, genetic factors seem to be predominant [12]. Although not all causes of ASD are known yet, it is estimated that up to 40% of cases related to genetic influences can be identified [13, 14]. The remaining percentage is possibly a result of other factors such as prenatal, perinatal, and postnatal environmental factors [15].

In this sense, the causes of ASD might be considered highly genetic due to multiple patterns of family inheritance and the occurrence of many variations. It is currently known that men have a higher incidence of ASD, about four times more than women [16].

Experimental and clinical studies have identified more than 800 genes related to ASD, making it one of the most complex neurophysiological disorders [17]. In this sense, there is evidence of the importance of complex genetic factors composed of different forms of genetic variation in the etiology of ASD [18]. These include genes involved in intellectual disabilities, neuropsychiatric disorders, common pathways, ASD risk genes, multigene contributions from rare or common variations, DNA mutations, and environmental effects on gene expression and/or protein function [19].

The most affected genes encode proteins that are involved with chromatin remodeling and transcriptional regulation, cell proliferation, and mainly synaptic architecture and functionality [17].

An important study elucidated several genetic and non-genetic factors related to ASD. The genetic causes can be several, but the authors have highlighted the following characteristics: new mutations, rare and common genetic alterations, and also polymorphisms. The study states that several genes associated with ASD have already been listed. These genes listed by *SAFARI* (Simons Foundation Autism Research Initiative) are classified according to the risk of causing ASD and are subdivided into four different categories, according to the number of new mutations reported in the literature, namely syndromic S, category 1, category 2, and category 3 [20].

According to the number of new mutations, the first category to be listed is syndromic (S), which includes genes whose mutations carry a substantial risk for the occurrence of ASD, and other characteristics present in other disorders that can predict ASD. Category 1 predicts a high risk for the onset of ASD and is characterized by having at least three new mutations reported in the literature. Category 2 genes are those that have a strong risk of association with ASD and include at least two new mutations. Finally, category 3 genes are those that include the vast majority of genes and that may or may not be suggestive of the onset of ASD, having at least one new mutation [21].

While there are different mechanisms through which genetic factors may influence autistic behaviors and clinical variants of ASD, inflammation and immune activation, oxidative stress, hypoxia, and endocrine disorders are likely the most important contributors to atypical neurodevelopment [22]. In fact, the relevance of these factors may not be of the direct cause, and thus, sometimes they may be confused with genetic factors. Furthermore, current understanding is limited due to a paucity of research examining gene–environment interactions.

On the other hand, there is a growing awareness of the potential of environmental influences on ASD, which stands out as a topic of great current scientific interest. In this regard, researchers have investigated several environmental risk factors that correlate with this pathology, including maternal and paternal age, fetal environment, perinatal and obstetric events, medications, nutritional events, smoking, and alcohol use [22].

With regard to biological environmental factors, the important factor of advanced paternal age (APA) has been associated with the reduced cortical thickness of the right posterior ventral cingulate cortex in ASD descendants [23].

Experiments performed in murine models confirmed that APA is associated with the development of ASD-like symptoms in offspring and with altered cortical morphology in male mice with APA [24, 25].

ASD-related behaviors were also observed in second-generation mice with older grandparents, indicating that APA-associated genetic and epigenetic changes are heritable [25].

Among the most researched environmental risk factors in ASD, perinatal ones are among the most difficult factors to be determined and predicted in advance. In the available literature, two comprehensive meta-analyses examined 60 obstetric factors and found statistically significant associations between the risk of ASD and umbilical cord complications, birth injury or trauma, multiple births, maternal hemorrhage, low birth weight, and neonatal anemia [26].

There is also evidence of the association between increased risk of autism and different factors, including cesarean delivery, induced delivery, fetal age less than 36 weeks, and fetal distress [15].

Such facts surely contribute to a better understanding of ASD during the first years of life, because derived from them, new biomarkers and new concepts in the neuropathology of ASD are possible to be observed in case ASD is considered to be a multifactorial disorder that affects several neuronal regions, and that will probably get worse, if not diagnosed during childhood.

3. Neurophysiology in ASD

The complex "machine" that orchestrates the entire body ordering is governed by active cells and neural circuits responsible for sensitivity, motricity, thoughts, ideas

and feelings, among others, and such functions are fully realized, enabling the totality of cognitive and motor movements. This complex system leads to the synaptic cleft, whose communication is not primarily electrical, but chemical. The neuron releases substance at its end to the bottom of the synaptic cleft, thus generating the so-called synapse, which is the chemical communication of neurons [27].

Substances that may act in different brain regions, such as acetylcholine, serotonin, and glutamate that enter the synaptic cleft are neurotransmitters that have different excitatory or inhibitory actions, critically involving impairments in particular aspects of inhibitory gamma-aminobutyric acid (GABA). In fact, in a study carried out with animal models was shown that there is a dysfunction in the signaling involving GABA, which is known to be the most important inhibitory neurotransmitter in the adult mammalian brain, possibly contributing to the clinical symptoms found in autistic patients [28].

GABA can inhibit neuronal excitation by activating two main receptors: GABAA, which are integral membrane ion channels, and GABAB, which are G protein-coupled ion channels. In patients diagnosed with Autism Spectrum Disorder, brain tissues show a reduction in the density of GABAA and GABAB receptors in the cingulate cortex region, and alterations in the morphology of the tracings, being related to a GABAergic imbalance between excitation and inhibition, involving the senses, memory, social and emotional processes [28].

GABA levels are relevant factors when referring to ASD, and polymorphisms in the receptors of GABA may be an explanation for this relationship. By evaluating the serum levels of GABA together with the genetic variants of GABAA receptor, it is possible to ascertain a strict agreement between high serum levels of GABA and the etiology of ASD [29]. Although it is embryonic, polymorphisms found in the GABAA receptors in the GABRB3, GABRG3, and GABRA5 subunits may be related to the appearance of ASD. Especially the mutations found in the rs4906902G and rs140679T subunits can confer substantial risk for the appearance of at least one deficit associated with ASD since these mutations alter the expression of these receptors [30].

GABAB receptors, on the other hand, play an important role in brain development. The activation of presynaptic receptors of this type is related to the inactivation of neurotransmitters and neuropeptides in the synaptic cleft. Moreover, GABAB receptors postsynaptic activation is related to the slow and long inhibition of the action potential. In autistic individuals, the amount of these receptors is reduced, which can cause a deficit in the migration and differentiation of new neurons, as well as a decrease in their production during corticogenesis. Another relevant factor is that the decrease in the expression of GABAB receptors also diminishes the protection they provide against insulin-like growth factor 1 (IGF-1), which can cause apoptosis of neurons, explained by the mechanism of autophosphorylation inhibition of the IGF-1 receptor and PI3 kinase/Akt inactivation [31].

Glutamate, on the other hand, known to be the most important excitatory neurotransmitter in the central nervous system, and to be associated with the regulation of excitatory/inhibitory balance, also plays an important role in neuronal migration and differentiation, as well as in synaptogenesis. There are three main receptors associated with glutamate, but evidence suggests that α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and N-methyl-D-aspartate receptors (NMDARs) when mutated are strongly related to the appearance of ASD. Overexpression of the NR2A and NR2B subunits of the NMDAR receptor has been demonstrated in association with autism since such subunits cause excessive excitation of synaptic currents in the receptors, which may increase postsynaptic plasticity,

causing an imbalance in the E/I system. In the second receptor reported, AMPAR, modifications were identified in the AMPAR GluA2 subunit, which also causes excessive excitability when associated with ASD. In other words, a high release of glutamate in the synaptic cleft may be strongly associated with ASD [32].

Still, glutamate is related to memory functions and cognitive performance; as a confirmation of this relation, however, its excess has been reported to act as a potent neurotoxin that might cause neuronal death and may also be related to neurological disorders [33]. Through a meta-analysis, a brief relationship was found between high levels of glutamate and ASD, as autistic symptoms were more evident in patients with high levels of glutamate, demonstrating, thus, that glutamate is a potent biomarker for the disorder [34].

Another system related to changes that can be associated with ASD corresponds to the serotonergic system. Serotonin or 5-HT is an important neurotransmitter in neuronal growth, synaptogenesis, differentiation, as well as neurogenesis [35]. 5-HT can be produced essentially in two identified places in the organism: in the central nervous system (CNS), by the serotonergic neurons of the raphe nucleus, and in the gastrointestinal tract by the enterochromaffin cells. Serotonin produced by enterochromaffin cells is predominantly the so-called peripheral serotonin, 99% of which is stored inside platelets with the help of the 5-HT transporter (SERT), and then stored in vesicles by the vesicular monoamine transporter (VMAT2). Both transporters are modulated by protein complexes present in the blood, such as αIIbβ3 and 5-HT2A receptors [36].

The marked effects of serotonin on the CNS are already well known in the literature, such as mood control, states of happiness, sleep modulation, and changes in pain perception; therefore, changes that affect serotonergic neurotransmission and cause a decrease in serotonin bioavailability are strongly associated with disorders such as depression and anxiety [37].

Interestingly, in autistic individuals, especially children, there are many reports of hyperserotonemia, characterized by an elevated amount of serotonin, mainly peripheral. This factor may lead to changes in the growth trajectory of serotonin synthesis in the brain [38]. Such a condition may be associated with an increased plasma concentration of SERT in platelets, as well as changes in affinity for 5-HT receptors [38].

In experimental models of ASD, it has been observed that cases of hyperserotonemia worsen cognitive deficits and behavioral patterns, and they may also affect immunomodulatory function, significantly increasing brain inflammation and oxidative stress. Such effects are reported because serotonin directly or indirectly impacts the levels of substances such as BDNF, pCREB/CREB, IL-10, GSH, TNF-α, IL-6, and TBARS, associated with inflammation and oxidative stress [39].

3.1 New concepts of ASD Neuropathology

Inserted into the traditional concepts of ASD, new updates appear on the subject, which improves the understanding and how the treatment will be given to the patient with ASD. Performing a brief search in the Medline/Pubmed database up to August 2022, there were 49,828 articles published in the last 5 years with the descriptor (autism spectrum disorder), but when the advanced search was used to describe the pathology of ASD, 2141 results were found in the same period of publication, what demonstrates the scientific community's great interest in understanding the factors that trigger this disorder.

As of 2017, new concepts emerged for ASD analysis that could not be accessed only with neuroimaging studies, such as differentiation and migration processes,

neuronal morphology, and cytoarchitectural changes in the nervous system. Based on this, it was elucidated that there are disorganizations in the white and gray matter of the brain and that they are associated with cognitive and judgment difficulties. In individuals with ASD, these changes cause dysplasia and heterotopia, which can be detected concurrently or in isolation [40]. Furthermore, in this group there is a decrease in the expression of reelin, a protein necessary for maturation and migration during cortical lamination [41].

Regarding brain cytoarchitecture, there is an age-dependent increase in brain circumference size. In younger individuals, this macrocephaly may be related to minicolumnopathy, that is, to an abnormal number of connections that neurons make with the neocortex. In patients with ASD, a greater number of minicolumns can be found, but with reduced size in 9, 21, and 22 Brodmann's areas; however, these changes are visible in the primary visual cortex, suggesting that they are regionally specific. Finally, there is also a significant increase in neuropil, non-myelinated axons, synapses, and glial cells in the frontopolar region, but not in the motor and somatosensory cortex [42].

Relating these facts, it could be verified that neuropathological disorders are linked to dysfunctions in the membrane of neurons and autophagy, caused by defects in the synthesis of GTPases, induced by Xq28 mutations located in the RAB39B gene. Such changes are related to defects in neuronal development, what can lead to macrocephaly, Parkinson's, and ASD [43].

Corresponding to this, a review published in the International Journal of Molecular Sciences tried to discuss the genetic, epigenetic, and environmental factors that may contribute to the pathogenesis of ASD, and how these factors alter brain neurophysiology. The authors confirm what has already been elucidated about changes in synaptic cytoarchitecture and their functions. These Changes, in turn, are mainly related to the formation of dendritic spines [17].

Dendritic spines are small actin-rich membranous protrusions present on a dendrite, responsible for the postsynapse of various excitatory impulses. Therefore, alterations that cause an increase or decrease in its size, or even alterations in the production of actin, can be the factors that alter the normal functioning of synapses, and consequent learning and memory mechanisms, that is, they can be a risk and can be observed in patients with neurological disorders such as ASD. Furthermore, it has been elucidated that those alterations in postsynaptic density proteins, which include cell adhesion proteins and cytoskeletal proteins, may be associated with ASD [17].

Neurexins (NRXN) and neuroligins (NLGN) are adhesion proteins between cells, present in the membrane of presynaptic neurons and which are crucial for the functioning of the synapses; however, in individuals with ASD there is a loss in the function of the NRX1 protein variant, what was confirmed in a study in animals, as they presented symptoms common to ASD [44]. In addition, there is a decrease in the amount of an adhesion protein between glia cells and neurons, CNTNAP2, which according to a study in mice, is also related to ASD [45].

Another group of proteins that may be related whenever variants arise are the scaffold proteins. Scaffold proteins or SHANK proteins are dense postsynaptic proteins that connect neurotransmitter receptors, ion channels, and other membrane proteins to the actin cytoskeleton and signaling proteins. Deletions that occur, therefore, in the genes that synthesize these proteins can cause malfunction or even shut down in their synthesis. These deletions in the proteins of the SHANK family, in turn, determine the Phelan–McDermid syndrome, and are characterized by cognitive problems, epilepsy, and ASD. It was also identified that in individuals with ASD, loss of protein function due to mutations in the SHANK3 gene is more frequent than in other family

genes [46]. Finally, in patients with ASD, there are mutations that can affect ion channels. The most common mutations occur in the following genes: CACNA1C, CACNB2, SCN1A, VDAC, and also in genes encoding potassium channels [47].

By utilizing recent studies, an interesting systematic review elucidated the role of microglia in brain development and how its dysfunctions may be important in the development of brain disorders, such as ASD, which demonstrates another factor to be considered for the diagnostic evaluation of the disease. However, further studies are still needed to confirm this event [48].

Another review was discussed about the neuronal imaging research from a structural, functional, and molecular perspective in order to have a more accurate diagnosis of ASD. Based on the evaluation of several studies, four main association factors were identified, namely exaggerated synaptic pruning, anomalous gyrification, interhemispheric connectivity, and glutamate/GABA imbalance. These factors, according to the researchers, are mitigated factors, but they make a difference in the multifactorial analysis of the disease, what can be a tool to improve the diagnosis in the future and how the pharmacological intervention will take place [49].

From a genetic point of view, researchers have demonstrated progress by using brain organoids to elucidate the genetic basis of certain neurodevelopmental disorders, such as ASD [50].

Organoid models of the human brain tried to identify and specify the development of disorders resulting from three risk genes for ASD: SUV420H1, ARID1B and CHD8, by using RNA sequence for the analysis of these cells. All three of these induced mutations confer the asynchronous development of two main neuronal lineages in GABA release and deep layer excitatory projection neurons, which according to the study, were contributing factors in the neuropathology of ASD [51].

In experimental research, researchers evaluated the mutations in an induced model of ASD and whether the displayed phenotypes are consistent with the symptoms of ASD. In this sense, a critical risk of these genetic factors for the etiology of ASD was suggested. Furthermore, applied neuroimaging identified common synaptic deficiencies in the neocortex, with specific mutations in neural circuitry [52].

With the neuroimaging analysis performed on human babies, it is possible to identify that in groups with ASD, there are smaller bilateral accumbens nuclei and larger cerebral ventricles. In addition, less thickness has been identified in the caudal anterior cingulate cortex and greater thickness in the right medial orbitofrontal cortex. These factors are independent of age, gender, and gestational age, suggesting that there are magnetic resonance imaging biomarkers that can predict the development of ASD, and that can help in a better diagnosis of the disorder [53].

Based on new advances and what has been elucidated here, new biomarkers have arisen for a better understanding of ASD neuropathology. It is worth mentioning that recent research in the area does not invalidate or discredit previous well-designed concepts about ASD. New concepts involving ASD neurophysiology are added to those already described, so that a more effective diagnosis of the disorder is expected, as well as more integrative and efficient forms of treatment.

4. Updates on ASD Treatments

The diagnosis of ASD is predominantly based on the observation of atypical behaviors, with criteria of persistent deficits in social communication and restricted and repetitive behavior patterns [19, 54].

Four criteria have been considered for the diagnosis of ASD: persistent impairment in social communication and social interaction (Criterion A), restricted and repetitive patterns of behavior, interests, or activities (Criterion B). These symptoms are present from early childhood and limit or impair daily functioning (Criteria C and D). The classification is made by the level of severity of the disorder, according to the criteria mentioned above, and through the necessary support to the person with ASD [6].

Intellectual disability is present in 70% of the population with ASD, with 29.3% of individuals having mild/moderate disability and 38.5% having severe/profound disability [55]. Diagnosis occurs from 3 years of age, but therapeutic measures should be taken whenever marked changes are observed by the multidisciplinary team [56].

With the advent of new research and technologies, recent studies on ASD have gained prominence in the scientific community, regarding management and treatments for this population. In this sense, transcranial direct current electrical stimulation (tDCS) proved to be a safe, well-tolerated, and low-cost technique with tDCS occurring through scalp electrodes that modulate regional cortical excitability [57].

A study with 18 autistic 6–14-year-old children, analyzed the effects of tDCS in improving balance and found that those who received about 1.5 m over the left M1 for 20 minutes in conjunction with motor exercises, considerably increased the static and dynamic balance in a few weeks [58].

Another study, involving 6 adults with ASD in ages ranging from 18 to 58 years, with the anode electrode being placed over the right parietal temporal lobe (PC6), revealed that there was a more significant improvement in the emotional verbal fluency of the individuals [59].

Another promising research proceeds from gene therapy to help elucidate and look for new treatments in the future. An important factor is that ASD may have a single clinical or syndromic phenotype. In the latter case, ASD is indicative of a developmental disorder that includes different phenotypes, such as epilepsy, intellectual disability, and dimorphic aspects [60]. For non-syndromic ASD, there is genetic evidence for a polygenic or multifactorial architecture, and disease risk is expected to be determined by a combination of multiple environmental and genetic reasons [61].

In a recent study, 11 single-gene ASD syndromes were selected, validated by animal models, and current gene therapies. Due to the wide range of possibilities, it was decided on the gene and mutation therapy study. Gene therapies that have a transient effect, including ASOs, ncRNA, and RNA-editing leave the genome unedited and will require repeated dosing; nevertheless, they may have the primacy of being controllable and reversible. The accurate diagnosis of DNA and, consequently, the accurate prediction of the consequences of the mutation will hopefully be able to elucidate and help in gene therapies soon [62].

In parallel to this, some treatments are already widely discussed or are already available at the population level. In this sense, recent research on ASD has gained prominence in the scientific community regarding treatments with cannabidiol.

Cannabidiol comes from *Cannabis sativa*, a plant that contains two main cannabinoids: tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is psychoactive and can cause anxiety and psychosis. CBD is non-psychoactive and has anxiolytic, antipsychotic, anti-inflammatory and antioxidant potential, with a high threshold of toxicity [63]. Cannabidiol has multiple targets, regulating the performance of glutamate and GABA, thus, influencing the excitatory and inhibitory signaling pathways, respectively [64].

In fact, there is a growing interest in the use of Cannabis, and particularly cannabidiol, as a treatment for mental health and neurodevelopmental disorders, such as

ASD. In this regard, cannabidiol is known to have important neuroprotective effects on addiction, cognition, and negative affect [65].

The use of cannabidiol for the treatment of ASD has been reported as a well-tolerated, safe, and effective option for the relief of symptoms, including seizures, stereotypies, depression, restlessness, and aggression [66].

According to a recent study, more than 80% of children with ASD treated with cannabidiol had significant or moderate improvement in symptoms and cognitive difficulties [67].

In this sense, researchers evaluated the intervention with Cannabis rich in cannabidiol, in 60 children with ASD, who had severe behavioral problems. After treatment with 10 mg/kg/day of Cannabis oil, behavioral flare-ups improved in 61% of patients [68]. In another recent study, 53 children were given Cannabis extract for 66 days, and attacks of self-harm and anger improved by 67.6%, hyperactivity improved by 68.4%, sleep problems improved by 71.4%, anxiety by 47.1%, and adverse effects such as drowsiness and change in appetite were mild. Thus, the authors suggest that cannabidiol may be effective in improving ASD symptoms [69].

The new treatments, whether with the use of electrostimulation technologies, or with the use of phytotherapy drugs, are shown today to be effective and safer alternatives for patients with ASD, which demonstrates great benefit, as it is possible to guarantee a better quality of life, an element that traditional pharmacological therapies might not achieve.

5. Conclusion

ASD is a set of heterogeneous conditions of neurological development, whose elucidation is still partial in the scientific/medical literature. With the constant increase in diagnosed cases, research has been carried out in human and experimental models. In fact, findings on risk factors and neurophysiological functioning in ASD are fundamentally important to understand this disorder and to enable innovation in satisfactory interventions. There are significant advances in etiology, diagnosis, and neural functions in ASD, as well as effective and promising treatments such as gene therapies, transcranial direct current electrical stimulation (tDCS), and the use of cannabis/cannabidiol.

While there are clear challenges with regard to elucidating the complex neurophysiology of autism, it is also clear that surprising advances are being made, as shown in the contributions of this chapter. Such findings could potentially contribute to new intervention research looking forward to alleviating symptoms in the ASD population.

Conflicts of interest

The authors declare no conflicts of interest.

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References

[1] Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J. Autism spectrum disorder. Lancet. 2018;**392**:508-520. Available from: https://pubmed.ncbi.nlm.nih.gov/30078460/. [Accessed August 23, 2022]

[2] Fusar-Poli L, Cavone V, Tinacci S, Concas I, Petralia A, Signorelli MS, et al. Cannabinoids for people with ASD: A systematic review of published and ongoing studies. Brain Sciences. 2020;**10**:1-18. Available from: https://pubmed.ncbi.nlm.nih.gov/32825313/. [Accessed August 23, 2022]

[3] Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. Prevalence of autism spectrum disorder among children aged 8 years – Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014. Morbidity and Mortality Weekly Report. 2019;**67**:1-23. Available from: https://www.cdc.gov/mmwr/volumes/67/ss/ss6706a1.htm. [Accessed August 23, 2022]

[4] Reynoso C, Rangel MJ, Melgar V. El trastorno del espectro autista: aspectos etiológicos, diagnósticos y terapéuticos. Revista Médica del Instituto Mexicano del Seguro Social. 2017;**55**:214-222

[5] Hu VW, Devlin CA, Debski JJ. ASD phenotype—genotype associations in concordant and discordant monozygotic and dizygotic twins stratified by severity of autistic traits. International Journal of Molecular Sciences. 2019;**20**:3804-3804. Available from: /pmc/articles/PMC6696087/. [Accessed August 23, 2022]

[6] American Psychiatric Association, editor. DSM-5 - Manual Diagnóstico e Estatístico de Transtornos Mentais. 5th ed. Arlington, TX: Artmed: American Psychiatric Association; 2013

[7] Matsuzaki H, Iwata K, Manabe T, Mori N. Triggers for autism: Genetic and environmental factors. Journal of Central Nervous System Disease. 2012;**4**:27. Available from: /pmc/articles/PMC3619552/. [Accessed August 23, 2022]

[8] Posar A, Visconti P. Autismo em 2016: necessidade de respostas. Jornal de Pediatria. 2017;**93**:111-119. Available from: http://www.scielo.br/j/jped/a/WWH8xDrXxL3KTLFhL7vX9Px/abstract/?lang=pt. [Accessed August 23, 2022]

[9] Ribeiro I, Freitas M, Oliva-Teles N. As Perturbações do Espectro do Autismo – Avanços da Biologia Molecular. Nascer e Crescer. 2013;**22**(1):19-24. Available from: http://repositorio.chporto.pt/handle/10400.16/1487. [Accessed August 23, 2022]

[10] Prochazka A. Neurophysiology and neural engineering: A review. Journal of Neurophysiology. 2017;**118**:1292-1309. Available from: https://pubmed.ncbi.nlm.nih.gov/28566462/. [Accessed August 23, 2022]

[11] Foxe JJ, Molholm S, Baudouin SJ, Wallace MT. Explorations and perspectives on the neurobiological bases of autism spectrum disorder. The European Journal of Neuroscience. 2018;**47**:488-496. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/ejn.13902. [Accessed August 23, 2022]

[12] Nadia B, Ridha M, B. Ahlem, Mohamed Bechir H, Habiba C. Autism: An overview of genetic aetiology. Tunis Med. 2008;**86**:573-578

[13] Froehlich-Santino W, Londono Tobon A, Cleveland S, Torres A,

Phillips J, Cohen B, et al. Prenatal and perinatal risk factors in a twin study of autism spectrum disorders. Journal of Psychiatric Research. 2014;**54**:100-108. Available from: https://pubmed.ncbi.nlm.nih.gov/24726638/. [Accessed August 23, 2022]

[14] Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, et al. Genetic heritability and shared environmental factors among twin pairs with autism. Archives of General Psychiatry. 2011;**68**:1095-1102. Available from: https://pubmed.ncbi.nlm.nih.gov/21727249/. [Accessed August 23, 2022]

[15] Wang C, Geng H, Liu W, Zhang G. Prenatal, perinatal, and postnatal factors associated with autism: A meta-analysis. Medicine. 2017;**96**:e6696-e6696. Available from: /pmc/articles/PMC5419910/. [Accessed August 23, 2022]

[16] Tran KT, Le VS, Bui HTP, Do DH, Ly HTT, Nguyen HT, et al. Genetic landscape of autism spectrum disorder in Vietnamese children. Scientific Reports. 2020;**10**:1-11. Available from: /pmc/articles/PMC7081304/. [Accessed August 23, 2022]

[17] Masini E, Loi E, Vega-Benedetti AF, Carta M, Doneddu G, Fadda R, et al. An overview of the main genetic, epigenetic and environmental factors involved in autism spectrum disorder focusing on synaptic activity. International Journal of Molecular Sciences. 2020;**21**:1-22. Available from: /pmc/articles/PMC7663950/. [Accessed August 29, 2022]

[18] Devlin B, Scherer SW. Genetic architecture in autism spectrum disorder. Current Opinion in Genetics & Development. 2012;**22**:229-237. Available from: https://pubmed.ncbi.nlm.nih.gov/22463983/. [Accessed August 23, 2022]

[19] Masi A, DeMayo MM, Glozier N, Guastella AJ. An overview of autism spectrum disorder, heterogeneity and treatment options. Neuroscience Bulletin. 2017;**33**:183. Available from: /pmc/articles/PMC5360849/. [Accessed August 23, 2022]

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

[21] Satterstrom FK, Kosmicki JA, Wang J, Breen MS, De Rubeis S, An JY, et al. Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. Cell. 2020;**180**:568. Available from: /pmc/articles/PMC7250485/. [Accessed August 23, 2022]

[22] Bölte S, Girdler S, Marschik PB. The contribution of environmental exposure to the etiology of autism spectrum disorder. Cellular and Molecular Life Sciences. 2018;**76**:1275-1297. Available from: https://link.springer.com/article/10.1007/s00018-018-2988-4. [Accessed August 29, 2022]

[23] Kojima M, Yassin W, Owada K, Aoki Y, Kuwabara H, Natsubori T, et al. Neuroanatomical correlates of advanced paternal and maternal age at birth in autism spectrum disorder. Cerebral Cortex. 2019;**29**:2524-2532. Available from: https://academic.oup.com/cercor/article/29/6/2524/5003434. [Accessed August 23, 2022]

[24] Foldi CJ, Eyles DW, McGrath JJ, Burne THJ. Advanced paternal age is associated with alterations in discrete behavioural domains and cortical neuroanatomy of C57BL/6J mice. The European Journal of Neuroscience. 2010;**31**:556-564. Available from: https://

pubmed.ncbi.nlm.nih.gov/20105239/. [Accessed August 23, 2022]

[25] Sampino S, Juszczak GR, Zacchini F, Swiergiel AH, Modlinski JA, Loi P, et al. Grand-paternal age and the development of autism-like symptoms in mice progeny. Translational Psychiatry. 2014;**4**:e386. Available from: https://www.nature.com/articles/tp201427. [Accessed August 23, 2022]

[26] Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: Comprehensive meta-analysis. The British Journal of Psychiatry. 2009;**195**:7-14. Available from: https://www.cambridge.org/core/journals/the-british-journal-of-psychiatry/article/prenatal-risk-factors-for-autism-comprehensive-metaanalysis/0D63EE57942E9A0CC312EA30025A9DD2. [Accessed August 23, 2022]

[27] Lopes ACP, Rosa LC, De R, Beleboni O, Pereira RNR, De Vasconcelos CAC, et al. Aspectos moleculares da transmissão sináptica. Medicina (Ribeirão Preto). 1999;**32**:167-188. Available from: https://www.revistas.usp.br/rmrp/article/view/12692. [Accessed August 29, 2022]

[28] Kerche-Silva LE, Camparoto ML, Rodrigues FV. As alterações genéticas e a neurofisiologia do autismo. SaBios - Revista de Saúde e Biologia [Internet]. 2020;15:40-56. Available from: https://revista2.grupointegrado.br/revista/index.php/sabios/article/view/2932. [Accessed August 29, 2022]

[29] Saha S, Chatterjee M, Dutta N, Sinha S, Mukhopadhyay K. GABA receptor SNPs and elevated plasma GABA levels affect the severity of the Indian ASD probands. Journal of Molecular Neuroscience. 2022;**72**:1300-1312. Available from: https://pubmed.ncbi.nlm.nih.gov/35562522/. [Accessed August 29, 2022]

[30] Adak P, Sinha S, Banerjee N. An association study of gamma-aminobutyric acid type A receptor variants and susceptibility to autism spectrum disorders. Journal of Autism and Developmental Disorders. 2021;**51**:4043-4053. Available from: https://pubmed.ncbi.nlm.nih.gov/33442857/. [Accessed August 29, 2022]

[31] Oblak AL, Gibbs TT, Blatt GJ. Decreased GABAB receptors in the cingulate cortex and fusiform gyrus in autism. Journal of Neurochemistry. 2010;**114**:1414. Available from: /pmc/articles/PMC2923229/. [Accessed August 29, 2022]

[32] Marotta R, Risoleo MC, Messina G, Parisi L, Carotenuto M, Vetri L, et al. The neurochemistry of autism. Brain Sciences. 2020;**10**:163-163. Available from: https://pubmed.ncbi.nlm.nih.gov/32182969/. [Accessed August 29, 2022]

[33] Yang P, Chang C-L. Glutamate-mediated signaling and autism spectrum disorders: Emerging treatment targets. Current Pharmaceutical Design. 2014;**20**:5186-5193. Available from: https://pubmed.ncbi.nlm.nih.gov/24410563/. [Accessed August 29, 2022]

[34] Zheng Z, Zhu T, Qu Y, Mu D. Blood glutamate levels in autism spectrum disorder: A systematic review and meta-analysis. PLoS One. 2016;**11**:158688. Available from: /pmc/articles/PMC4938426/. [Accessed August 29, 2022]

[35] Howes OD, Rogdaki M, Findon JL, Wichers RH, Charman T, King BH, et al. Autism spectrum disorder: Consensus guidelines on assessment, treatment and

research from the British Association for Psychopharmacology. Journal of Psychopharmacology. 2018;**32**:3. Available from: /pmc/articles/PMC5805024/. [Accessed August 29, 2022]

[36] Gabriele S, Sacco R, Persico AM. Blood serotonin levels in autism spectrum disorder: A systematic review and meta-analysis. European Neuropsychopharmacology. 2014;**24**:919-929. Available from: https://pubmed.ncbi.nlm.nih.gov/24613076/. [Accessed August 29, 2022]

[37] Apresentada D, Maria P, Glória BA. Determinação de precursores da serotonina - triptofano e 5-hidroxitriptofano - em café por clae-par iônico. Universidade Federal de Minas Gerais; 2008. Available from: https://repositorio.ufmg.br/handle/1843/MBSA-7JZM6L. [Accessed August 29, 2022]

[38] Katsui T, Okuda M, Usuda S, Koizumi T. Kinetics of 3H-serotonin uptake by platelets in infantile autism and developmental language disorder (including five pairs of twins). Journal of Autism and Developmental Disorders. 1986;**16**:69-76. Available from: https://pubmed.ncbi.nlm.nih.gov/3957859/. [Accessed August 29, 2022]

[39] Luhach K, Kulkarni GT, Singh VP, Sharma B. Effect of papaverine on developmental hyperserotonemia induced autism spectrum disorder related behavioural phenotypes by altering markers of neuronal function, inflammation, and oxidative stress in rats. Clinical and Experimental Pharmacology & Physiology. 2021;**48**:614-625. Available from: https://pubmed.ncbi.nlm.nih.gov/33480092/. [Accessed August 29, 2022]

[40] Pagnamenta AT, Wing K, Akha ES, Knight SJL, Bölte S, Schmötzer G, et al. A 15q13.3 microdeletion segregating with autism. European Journal of Human Genetics. 2009;**17**:687-692. Available from: https://pubmed.ncbi.nlm.nih.gov/19050728/. [Accessed August 29, 2022]

[41] Camacho J, Ejaz E, Ariza J, Noctor SC, Martínez-Cerdeño V. RELN-expressing neuron density in layer I of the superior temporal lobe is similar in human brains with autism and in age-matched controls. Neuroscience Letters. 2014;**579**:163-167. Available from: https://pubmed.ncbi.nlm.nih.gov/25067827/. [Accessed August 29, 2022]

[42] Varghese M, Keshav N, Jacot-Descombes S, Warda T, Wicinski B, Dickstein DL, et al. Autism spectrum disorder: Neuropathology and animal models. Acta Neuropathologica. 2017;**134**:537. Available from: /pmc/articles/PMC5693718/. [Accessed August 29, 2022]

[43] Tang BL. RAB39B's role in membrane traffic, autophagy, and associated neuropathology. Journal of Cellular Physiology. 2021;**236**:1579-1592. Available from: https://pubmed.ncbi.nlm.nih.gov/32761840/. [Accessed August 29, 2022]

[44] Südhof TC. Neuroligins and neurexins link synaptic function to cognitive disease. Nature. 2008;**455**:903-911. Available from: https://pubmed.ncbi.nlm.nih.gov/18923512/. [Accessed August 29, 2022]

[45] Peñagarikano O, Abrahams BS, Herman EI, Winden KD, Gdalyahu A, Dong H, et al. Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. Cell. 2011;**147**:235-246. Available from: https://pubmed.ncbi.nlm.nih.gov/21962519/. [Accessed August 29, 2022]

[46] Leblond CS, Nava C, Polge A, Gauthier J, Huguet G, Lumbroso S, et al.

Meta-analysis of SHANK mutations in autism spectrum disorders: A gradient of severity in cognitive impairments. PLoS Genetics. 2014;**10**:e1004580-e1004580. Available from: https://pubmed.ncbi.nlm.nih.gov/25188300/. [Accessed August 29, 2022]

[47] Schmunk G, Gargus JJ. Channelopathy pathogenesis in autism spectrum disorders. Frontiers Media. 2013;**4**: 222-222. Available from: /pmc/articles/PMC3817418/. [Accessed August 29, 2022]

[48] Lukens JR, Eyo UB. Microglia and neurodevelopmental disorders. Annual Review of Neuroscience. 2022;**45**: 425-445. Available from: https://pubmed.ncbi.nlm.nih.gov/35436413/. [Accessed August 29, 2022]

[49] Rafiee F, Rezvani Habibabadi R, Motaghi M, Yousem DM, Yousem IJ. Brain MRI in autism spectrum disorder: Narrative review and recent advances. Journal of Magnetic Resonance Imaging. 2022;**55**:1613-1624. Available from: https://pubmed.ncbi.nlm.nih.gov/34626442/. [Accessed August 29, 2022]

[50] Trujillo CA, Muotri AR. Brain organoids and the study of neurodevelopment. Tendências em Med Mol. 2018;**24**:982-990. Available from: https://pubmed.ncbi.nlm.nih.gov/30377071/

[51] Paulsen B, Velasco S, Kedaigle AJ, Pigoni M, Quadrato G, Deo AJ, et al. Autism genes converge on asynchronous development of shared neuron classes. Nature. 2022;**602**:268-273 Available from: https://pubmed.ncbi.nlm.nih.gov/35110736/ [Accessed August 29, 2022]

[52] Terashima H, Minatohara K, Maruoka H, Okabe S. Imaging neural circuit pathology of autism spectrum disorders: Autism-associated genes, animal models and the application of in vivo two-photon imaging. Reproductive System and Sexual Disorders. 2022;**71**:I81-I99. Available from: https://pubmed.ncbi.nlm.nih.gov/35275183/. [Accessed August 29, 2022]

[53] Shiohama T, Ortug A, Warren JLA, Valli B, Levman J, Faja SK, et al. Small nucleus accumbens and large cerebral ventricles in infants and toddlers prior to receiving diagnoses of autism spectrum disorder. Cerebral Cortex. 2022;**32**:1200-1211. Available from: https://pubmed.ncbi.nlm.nih.gov/34455432/. [Accessed August 29, 2022]

[54] Muotri AR. Autism spectrum disorders: Challenges and perspectives. Developmental Neurobiology. 2018;**78**:431-433. Available from: https://pubmed.ncbi.nlm.nih.gov/29516662/

[55] De Moura M, Evêncio K, Cristina H, Menezes S, George Fernandes P. Transtorno do Espectro do Autismo: Considerações sobre o diagnóstico / Autism spectrum disorder: Diagnostic considerations. Revista de psicologia. 2019;**13**:234-251. Available from: https://idonline.emnuvens.com.br/id/article/view/1983. [Accessed August 24, 2022]

[56] Pinho Costa JLG, Maia LO, Orlandi-Mattos P, Villares JC, Fernandez Esteves MA. Neurobiologia da Cannabis: do sistema endocanabinoide aos transtornos por uso de Cannabis. Jornal Brasileiro de Psiquiatria. 2011;**60**:111-122. Available from: http://www.scielo.br/j/jbpsiq/a/sjLsV6Qg3S7YtQWnKqwnjWv/?lang=pt. [Accessed August 29, 2022]

[57] Hameed MQ, Dhamne SC, Gersner R, Kaye HL, Oberman LM, Pascual-Leone A, et al. Transcranial magnetic and direct current stimulation in children. Current Neurology and Neuroscience Reports. 2017;**17**:11-11. Available from: https://pubmed.ncbi.

nlm.nih.gov/28229395/. [Accessed August 24, 2022]

[58] Mahmoodifar E, Sotoodeh MS. Combined transcranial direct current stimulation and selective motor training enhances balance in children with autism spectrum disorder. Perceptual and Motor Skills. 2020;**127**:113-125. Available from: https://pubmed.ncbi.nlm.nih.gov/31744385/. [Accessed August 24, 2022]

[59] Esse Wilson J, Trumbo MC, Wilson JK, Tesche CD. Transcranial direct current stimulation (tDCS) over right temporoparietal junction (rTPJ) for social cognition and social skills in adults with autism spectrum disorder (ASD). Journal of Neural Transmission. 2018;**125**:1857-1866. Available from: https://pubmed.ncbi.nlm.nih.gov/30341695/. [Accessed August 24, 2022]

[60] Buescher AVS, Cidav Z, Knapp M, Mandell DS. Costs of autism spectrum disorders in the United Kingdom and the United States. JAMA Pediatrics. 2014;**168**:721-728. Available from: https://pubmed.ncbi.nlm.nih.gov/24911948/. [Accessed August 24, 2022]

[61] LeClerc S, Easley D. Pharmacological therapies for autism spectrum disorder: A review. Pharmacology & Therapeutics. 2015;**40**:389. Available from: /pmc/articles/PMC4450669/. [Accessed August 30, 2022]

[62] Weuring W, Geerligs J, BPC K. Gene therapies for monogenic autism spectrum disorders. Genes (Basel). 2021;**12**: 1667-1667. Available from: https://pubmed.ncbi.nlm.nih.gov/34828273/. [Accessed August 29, 2022]

[63] Campos AC, Fogaça MV, Scarante FF, Joca SRL, Sales AJ, Gomes FV, et al. Plastic and neuroprotective mechanisms involved in the therapeutic effects of cannabidiol in psychiatric disorders. Frontiers in Pharmacology. 2017;**8**:269-269. Available from: https://pubmed.ncbi.nlm.nih.gov/28588483/. [Accessed August 29, 2022]

[64] Pretzsch CM, Freyberg J, Voinescu B, Lythgoe D, Horder J, Mendez MA, et al. Effects of cannabidiol on brain excitation and inhibition systems: A randomised placebo-controlled single dose trial during magnetic resonance spectroscopy in adults with and without autism spectrum disorder. Neuropsychopharmacology. 2019;**44**:1398-1405. Available from: https://pubmed.ncbi.nlm.nih.gov/30758329/. [Accessed August 29, 2022]

[65] Chadwick B, Miller ML, Hurd YL. Cannabis use during adolescent development: Susceptibility to psychiatric illness. Frontiers in Psychiatry. 2013;**4**: 129-129. Available from: https://pubmed.ncbi.nlm.nih.gov/24133461/. [Accessed August 29, 2022]

[66] Oliveira ALM de, Shecaira TP, Rodrigues LM, Bueno GC, Bernardes N. Transtorno do espectro autista e tratamento com canabidiol: uma revisão bibliográfica / Autism spectrum disorder and cannabidiol treatment: A literature review. Brazilian Journal of Development; 2021 ;7:39445-39459. Available from: https://brazilianjournals.com/ojs/index.php/BRJD/article/view/28355. [Accessed August 30, 2022]

[67] Bar-Lev Schleider L, Mechoulam R, Saban N, Meiri G, Novack V. Real life experience of medical cannabis treatment in autism: Analysis of safety and efficacy. Scientific Reports. 2019;**9**:200-200. Available from: https://pubmed.ncbi.nlm.nih.gov/30655581/. [Accessed August 29, 2022]

[68] Barchel D, Stolar O, De-Haan T, Ziv-Baran T, Saban N, Fuchs DO, et al. Oral cannabidiol use in children with

autism spectrum disorder to treat related symptoms and co-morbidities. Frontiers Media. 2018;**9**:1521-1521. Available from: /pmc/articles/PMC6333745/. [Accessed August 29, 2022]

[69] Aran A, Cassuto H, Lubotzky A, Wattad N, Hazan E. Brief report: Cannabidiol-rich cannabis in children with autism spectrum disorder and severe behavioral problems–A retrospective feasibility study. Journal of Autism and Developmental Disorders. 2019;**49**:1284-1288. Available from: https://pubmed.ncbi.nlm.nih.gov/30382443/. [Accessed August 29, 2022]