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ANTERIOR CINGULATE CORTEX AND ITS RELATIONSHIP WITH AUTISM

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Abstract: This bibliographic study aims to discuss the relationship between Autism Spectrum Disorder (ASD) and the anterior cingulate cortex, understanding how it relates physiologically and anatomically. Being an underdiagnosed disease, especially in adults, autism is characterized by a lack of social interaction, as well as an increase in incidence worldwide, since the last reported studies. Analyzing the cortical areas involved in this process, the anterior cingulate stands out, since it controls the neurobiology of social relationships. Thus, based on theoretical references found in books and data search platforms, such as Pubmed, this research will analyze articles from 2017-2021, using as keywords: autism and anterior cingulate cortex, seeking to establish a relationship between the neurological structure and the syndrome, emphasizing the pathways involved in this process, as well as the interference in the social life of individuals based on these discoveries. To this end, we hope to understand the axis that involves these two components and whether there are ways of interfering in this process, in order to help in new propaedeutics about this disease, seeking to establish early and emphatic diagnoses and targeted treatments. The analysis showed that the anatomical area studied is related to autism, and it is hoped that this research will contribute to early diagnosis and more targeted treatment for this disorder, in order to improve the quality of life and promote the health of these individuals.
Keywords: Autism Spectrum Disorder; Central Nervous System; Frontal Cortex.

INTRODUCTION

Autism spectrum disorder (ASD) is a behavioural syndrome characterized by a different connectivity between the cortexes than usual, which results in difficulties in social interaction, cognition, the presence of repetitive movements and the main characteristic is stereotyped behaviour (OLIVEIRA et al, 2015; WENDEROTH N., 2018). According to the UN (2010), there are more than 70 million autistic people in the world, and this data is still far behind in Brazil, but there is an estimate that approximately 1% of the Brazilian population has this syndrome. It is therefore estimated that Brazil, with its 200 million inhabitants, has around 2 million autistic people.

Epidemiological studies have reported that in recent years, there has been an increase in the rate of autism globally, with several studies showing diverse etiologies on the subject, such as infections, the presence of specific substances, uterine causes, genetics, growth of specific neural areas and lifestyle habits (BRASIL, 2017, TRONTEL HG, et al, 2018; KANG S, et al, 2019; RAMAN MM, 2020).

Being an underdiagnosed disease in the majority of the population, since there are no specific tests to determine the diagnosis, it is currently only made on the basis of clinical observation and the application of general protocols, using the criteria described in the Diagnostic and Statistical Manual of the American Psychiatric Association, the DSM-V. The delay in diagnosis directly implies a more difficult treatment, because the progression of age guarantees the appearance of more neural receptors that destabilize the patient's cortex and the neural formation, without a proper approach, will be altered by this disease, which can guarantee different neural thicknesses and dimensions, this can also affect the depths between the sulci. (MATTOS et al, 2019; BLATT GJ, 2019; ANAGNOSTOU E, et al, 2021).

With this in mind, some questions have been raised: is this disorder related to the anterior cingulate cortex (ACC), where the Ba32 region (Broadmann: area 32) (MACHADO, 2014) is specifically located? Which neural abnormalities could explain the different symptoms? Are there ways of obtaining a better diagnosis of this disorder? Are there ways of creating a more precise therapeutic approach?

Therefore, the aim of this work is to understand the intrinsic relationship between the anterior cingulate cortex and autism spectrum disorder, based on an analysis of various studies. By understanding the correlation between this specific area and the neurotransmitters involved, we can investigate new therapeutic techniques to diagnose this syndrome early and assertively.

METHODOLOGY

SEARCH STRATEGY

A search will be made for articles on the *Pubmed* platform in order to find the relationship between the anterior cingulate cortex and autism spectrum disorder (ASD). Following this study, an integrative literature review will be carried out on the influence of this area on the disorder. The searches will be in journals found in the PubMed database, in articles published in the last 5 years (2017-2021). The keywords used will be "anterior cingulate cortex" and "autism" and full texts were used as filters.

STUDY SELECTION

The articles will be screened, after removing duplicates, by analyzing the following criteria: complete availability of the articles in English, Portuguese or Spanish. The publications retained will be assessed for eligibility, selecting only those that include the Anterior Cingulate Cortex as the target of the study, and those that relate the anatomical area only

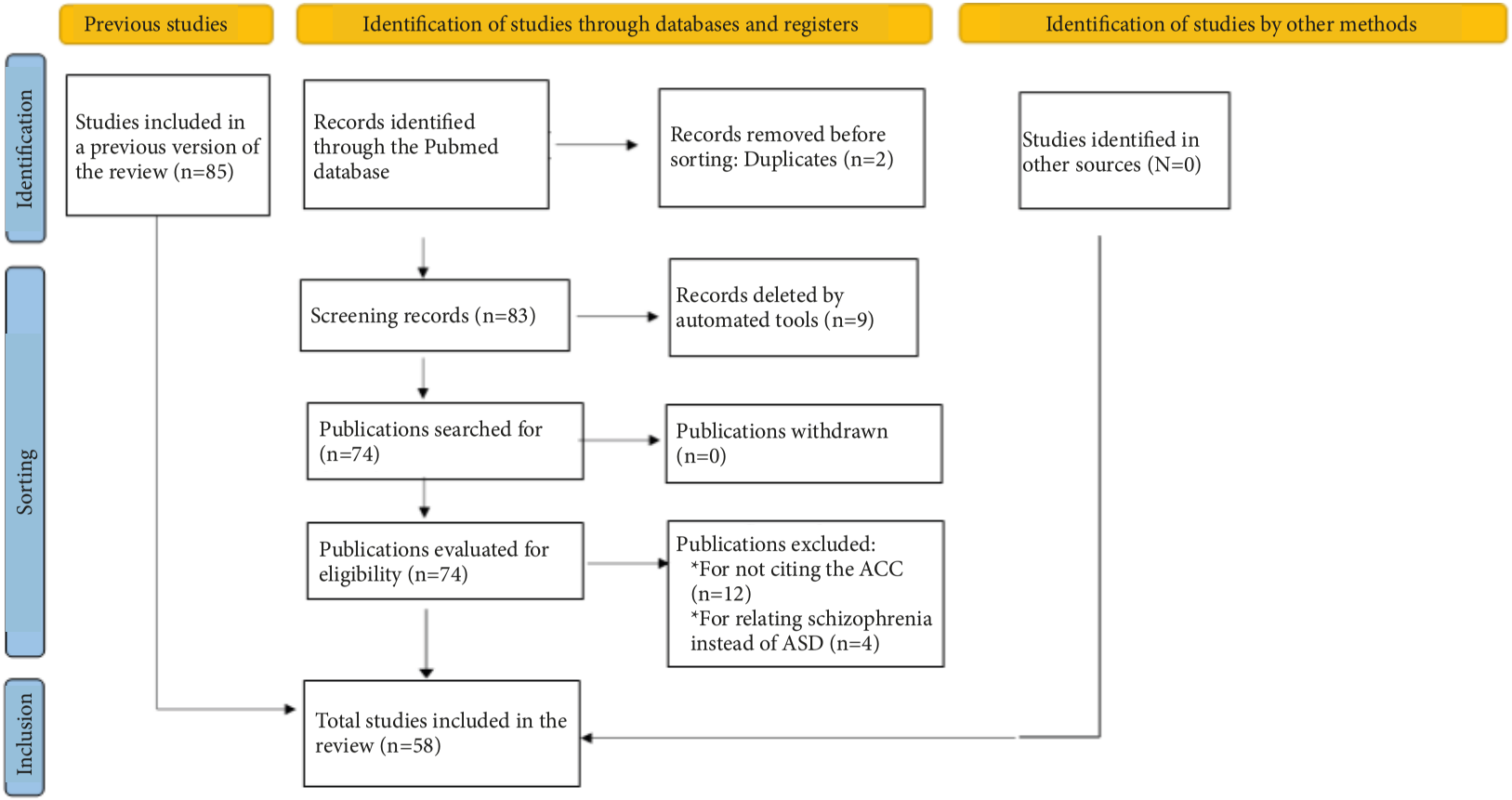

Figure 1. Flowchart adapted from *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA) showing the algorithm for selecting studies (PAGE et al, 2020).

to Autism Spectrum Disorder, excluding other disorders. The summary of the selection of articles is shown in Figure 1 and the articles included are shown in Table 1. (PAGE et al, 2020).

RESULTS AND DISCUSSION

Of the 74 articles analyzed, 58 showed an intrinsic relationship between the anterior cingulate cortex and autism spectrum disorder. 4 articles only mentioned the anatomical area of interest and analyzed another disorder and 12 articles did not mention the anterior cingulate cortex as the target of the study and were excluded from the analysis.

Taking into account the article by Caruana et al. (2018), the cingulate cortex includes the anterior, middle and posterior regions, called ACC, MCC and PCC, respectively, and the ACC is directly linked to error detection and cognitive mechanisms, something proven by Bubb et al (2018), through functional magnetic resonance imaging in rodents, which realized that the anterior cingulate cortex performs responses linked to emotion, reward, pain, conflict and error detection. Various alterations of the cingulate bundle have led to a wide variety of disorders related to the structure, shape and size of the tract, and in ASD there is reduced interconnectivity between the cingulate and anterior cingulate cortex, justifying the apathetic behavior and behavioral alterations. Therefore, it was noticed that a person with this disorder has an increased and free activity in the salience network, increasing the frequency of connection between neurons which makes the behavior inflexible to changes and slow adaptation (NORTHOFF G., 2019).

Several articles have shown the relationship between the symptoms of autism spectrum disorder and the areas related to this neurobiological process with different clinical presentations, which has justified the difficulty in making an early diagnosis and treatment (QI S.et al, 2020). This author, through the magnetic resonance imaging of individuals with the disorder and favorable clinical presentation, divided anatomical areas that are based on the socio-emotional pattern, the anterior cingulate cortex being one of them, and concluded that although the disorder has a common basis linked to social interaction, each clinical subtype has a specificity in the brain image, corroborating the affirmation of the symptomatological heterogeneity of ASD.

Thus, although there are various presentations of the symptoms, several articles focus on some predominant characteristic and explain it through image analysis. Starting with the relationship between ASD and lack of empathy, ZHAO et al (2021) define empathy as part of a neural network that demonstrates how a person reacts to another's pain, showing a genuine or feigned expression, something proven through functional magnetic resonance imaging of healthy adults exposed to video clips in which people were feeling or pretending to feel pain. It was found that the brain identifies differently when pain is really felt from when it is faked, concluding that this response is not just an automatic response to an emotion, but depends on people's real affections.

Schineider, et al (2020), studied the anatomical areas involved in this process. Through an experimental study, the author subjected six rats to a Pavlovian task (an experiment that allows us to analyze the behavioral influence of one group on another) and observed that the rats exhibited empathetic behavior when placed side by side. Considering that the ACC is responsible for this behavior, it was noticed that it modulates an expression according to the social context, something known as emotional mirroring. Therefore, a lack of ACC connectivity would lead to a lack of empathy (TAYLOR MJ, 2018;

LAIDE et al, 2019). These articles carried out an analysis of the magnetic resonance imaging data of 167 high-functioning adults with ASD and 195 controls, reporting the difference in anterior cingulate cortical thickness in the ASD group compared to the control group, being thinner in the former, in addition to investigating the correlation of this structure with social responsiveness demonstrating that individuals with thinner anterior caudal cingulate cortex tend to have lower social responsiveness, that is, they have a lower ability to understand the emotion of themselves and others. Thus, it can be concluded that individuals with ASD show privative empathic behavior, and that this characteristic is directly related to the Anterior Cingulate Cortex.

Another characteristic analyzed was altered socio-cognitive development in individuals with the disorder. This parameter was analyzed by MUNDY et al (2018) through a literature review, which brought together articles explaining how this process develops and how it differs in individuals with ASD. According to him, social response depends on a process called joint attention, which relates the ability to engage with people, i.e. social communication, as well as interpersonal relationships, developed from the age of five months. Taking this assumption into account, the articles concluded that the information gathered during infancy plays a substantial role throughout adulthood, and that the social development of the newborn depends on the consistency of interaction with their family through the modulation of neural networks. Combining this assumption with what is known about ASD, a deficiency of joint attention in the interactive process was noticed early on and considering that the anterior cingulate cortex in conjunction with dopaminergic systems are responsible for the integrated processing of internally motivated attention regulation information, according to the studies it would be logical for there to be less activation in children with ASD, but there is a need to analyze the processes through imaging tests

Considering that ASD is a multifactorial disease, genetics has a substantial influence on the analysis of this disorder (GUAN J. et al, 2021). Several studies have analyzed how genes influence the behavior of these individuals, delimiting which of them are important, seeking a therapy focused on excluding symptoms caused by these mutations (GUO et al, 2019).

The first gene studied was that of the SHANK3 protein, involved in the pathogenesis of several cases of autism. It first analyzed how this protein modulates the central nervous system. According to GUO et al (2019), it is responsible for regulating the manufacture of neurotransmitter receptors, the main one being AMPA. Thus, mutation of the gene leads to deletion of this protein, causing dendritic loss and consequently loss of synaptic transmission, especially in neurons present in the anterior cingulate cortex. Through fluorescent in situ hybridization and immunofluorescent staining of the aSHANK3 protein, it was found that the average length and thickness of the postsynaptic densities of these neurons were significantly lower, reducing the amplitude of excitatory synapses. This relationship caused socio-cognitive alterations in the mice subjected to this process, a characteristic also observed in ASD (GUO el, al 2019 and Huang Z, at al 2021).

In relation to the receptor in question, an optogenetic activation was tested in the modified mice, and an increase in social interaction was observed when stimulated, proving that this receptor is closely related to the process of interpersonal interaction. Taking into account that hypoactivity is related to dysfunction of the AMPA receptor, the study sought a drug, named CX546

(positive allosteric modulator compound) which, when injected subcutaneously into the mice, increased the amplitude of transmissions through AMPA, significantly increasing synaptic transmission, and could be an acceptable therapy to reduce this specific symptomatology (GUO el, al 2019 and Huang Z, at al 2021).

In addition to this study, BUBB et al (2018) analyzed the mutation of the same SHANK3 gene in just one allele in heterozygous mice. Named SHANK3b, it was noticed that the main characteristic they presented was a lack of glutamatergic synapse, through the non-phosphorylation of a GSK-3β protein, which when phosphorylated inhibits the natural activity of GSK-3β. This protein is an abundant serine in the brain and is involved in various synapse and signaling mechanisms via glutamatergic receptors. When in low concentration, it decreases pPSD95 (a GSK-3β substrate) and glutamate channels, leading to synaptic defects that are important for social communication in mice, an important symptom in ASD. Therefore, the article also sought a possible therapy for this symptom, by injecting active GSK-3β into mice. It was found that there was a positive regulation, restoring the synaptic plasticity previously lost, significantly affecting social behavior, and could be used in the treatment of this pathology.

Still on this gene, Dunn, et al (2020) studied its haploinsufficiency, known as Phelan-McDermid. This syndrome manifests a phenotype of autism with intellectual disability, which results from an elevated excitation of pyramidal neurons in the anterior cingulate cortex, which have serotonin 5-HT1A receptors.

Based on this assumption of gene analysis, a study by CHIEN et al (2019) linked another gene, CNTNAP2, which encodes the CASPR2 protein responsible for grouping potassium channels in the ranvier node of neurons, promoting depolarization, as well as being involved in axonal development. When a deletion of the gene occurs, it promotes a mutation in this function, clinically showing up as social deficits, a symptom present in ASD. One of the changes caused by this mutation is related to presynaptic proteins known as neurexins (*Nrxn2α* gene). It was noticed that heterozygous deletions produced various phenotypes of autistic individuals and in homozygotes, gross alterations in the thickness of the cell layer were observed. In addition, in anatomical areas such as the anterior cingulate cortex and orbitofrontal cortex there was an increase in genetic deletion with a different axonal orientation, through demyelination (PERVOLARAKI et al, 2019).

Another allele is LMO4, analyzed according to ZHANG et al (2020), which is reduced in patients with autism. This gene has a dual function, the first being an endogenous inhibitor of the tyrosine phosphatase PTP1B, and this inhibition eliminates repetitive behaviors and neurodevelopmental disorders. Patients with autism have a deletion in the gene that eliminates tyrosine, causing it to accumulate. In addition, this gene is expressed in PV (parvalbumin) cortical interneurons. These are GABAergic and are responsible for filtering the information that reaches the cortex. The study in question analyzed the relationship between the gene and its responses in autism spectrum disorder. To do this, two mice were used. The first did not contain the PV interneuron, and its findings were the presence of stereotyped behavior and reduced social interaction. In order to understand how ablation of the gene affects the interneuron, electrophysiological properties were measured and an increase in excitability was observed, causing more inhibition than excitation. The other mice had ablation of tyrosine (PTP1B) and showed

normalized action potentials, preventing neurodevelopmental disorders. Therefore, the conclusion of this gene-related study is that, when LM04 acts in its normal state, it ensures inhibition of PTP1b and expression in PV interneurons, which prevent autism.

YAMAMOTO et al (2019) used male mice homozygous for the gene that transcribes the FABP3 protein. This is a fatty acid binding protein that is intensely present in the GABAergic inhibitory interneuron present in the anterior cingulate cortex of mice, as well as being a negative regulator of Gad67 mRNA expression, i.e. when it is present, it decreases transcription. Through detailed analysis of the neural tissues of mice, it was observed that FABP3 in autistic mice was more highly expressed, generating an increase in the release of GABA in the neurons of the anatomical area studied. The increased release of this neurotransmitter led to a general inhibition of functions, such as a basal decrease in glutamate. Glutamatergic hypoactivity is responsible for the lower interest reported in the mice in seeking out new activities (apathy). In addition, it has been reported that there is a hypomethylation of Gad67, decreasing the uptake of fatty acids and generating a delay in brain development.

The mutation in a gene can generate an inappropriate factor, named EPAC2, which has the function of regulating excitatory and inhibitory synapses in neurons, as it interferes with different vesicular transporters and this leads to a deficit in dendritic arborization within the cingulate cortex, which can negatively affect social interactions (PENZES P. et al, 2019).

Still on genetics (Zur G. et al 2019), realized that there are children with a disorder called neurofibromatosis type 1 (NF1), which has multiple structural and functional alterations in the central nervous system, resulting in neuropsychological cognitive abnormalities, as there is a decrease in cortical functional connectivity and a certain myelin dysfunction, so they are more likely to have intense ASD symptoms. According to Torre JB, et al (2020), there is a positive association between neuroticism and functional connectivity of the right amygdala-subgenual anterior cingulate cortex (sgACC) in carriers of the A rs3796863 allele. This allele is a possible biomarker because it is socially sensitive and is related to the development and maintenance of social anxiety and depression. In addition, this allele is responsible for the genetic variation of CD38, which interferes with the regulation of oxytocin secretion and is therefore related to autism spectrum disorders and social anxiety disorder.

Finally, there are genes related to the X chromosome. The first is FMR1, which promotes mutation of the fragile X mental retardation protein. This monogenic mutation is responsible for 5% of all autism cases. The protein regulates the expression of synaptic proteins, and when mutated decreases their expression, such as glycogen synthase kinase 3β (GSK-3β), which is responsible for connecting various signaling pathways in the anterior cingulate cortex. When it is mutated, these pathways do not promote their function, causing social dysfunction, which is present in this disorder. The experimental study used FMR1 mice *(HOU et al, 2021).*

In addition, there is the IQSEC2 *gene*, which is linked to the X chromosome and encodes a post-synaptic density protein located in dopamine excitatory synapses, as well as GABAergic receptors, involved in brain plasticity processes and in the formation of dendritic spines, and its mutation is involved in autism. Magnetic resonance imaging in mice showed that this alteration in the gene caused a reduction in the expression of gluA2 AMPA receptors, causing abnormal social behavior, clinically similar to ASD. Anatomically, the

mice showed an increase in the volume of the total brain, especially the cerebral cortex, as well as an increase in connectivity between the anterior cingulate cortex and the dorsomedial striatum. This process is associated with the deactivation of social rewards, causing impairments in communication. Therefore, it is concluded that these genes together bring a perspective that the anterior cingulate cortex is related to social behavior, being affected in pathologies such as Autism, with high levels of connectivity presenting normal levels of sociability, through a compensatory neural response, and decreased levels showing a reduction in this characteristic (LICHTMAN et al, 2021).

In addition to the genetic influence, Raman MM (2020) pointed out that environmental factors interfere in the development of this disorder, directly interfering with the thickness of the gray matter in the orbitofrontal cortex and anterior cingulate cortex, which contributes negatively to restrictive and repetitive behaviors. Estes ML. et al (2021), Dziabis JE, et al (2020) and Jiang J. et al (2020) made the relationship between pregnancy and the pathology studied. The first found that through exposure to a specific viral particle in the first and second trimesters of pregnancy there were tarnscriptomic alterations in the DE- PIWWIL2 and MGARP genes, which caused abnormal social and repetitive behaviors, while the second linked the use of neonatal lipopolysaccharide (LPS), which caused an increase in interneurons that regulate the excitatory/inhibitory balance within the ACC and a deficit in sociability and social discretion. Finally, Jiang J. et al (2020) observed that stress due to acute placental ischemia-hypoxemia in utero could induce permanent dysfunction in the developing brain and raise the possibility of persistent mitochondrial dysfunction as the link between transient intrauterine asphyxia and neurodevelopmental disorders such as autism and schizophrenia. This is due to the fact that it reduces cerebral perfusion and increases lactate concentrations, which alters the development of the anterior cingulate cortex.

Leaving the realm of epigenetics and entering the anatomy itself, other studies have linked changes in the white and gray matter affecting the anterior cingulate cortex with ASD, suggesting micro and macro-structural heterogeneity (PINSK et al, 2020). ZIKOPOULOS et al (2018) related the development of myelinated axons in the brains of post-mortem children, adolescents and adults with and without autism, using high-definition electron microscopy. With the knowledge of neural pathways and the information that axons in children with autism spectrum disorder are less myelinated, i.e. have a lower density, the aim was to analyze how this disease progresses, comparing typical postnatal development with children with ASD, noting that symptomatological changes occur when the disease manifests itself at a younger age. In addition, Muller et al (2019) observed that neurotypical adults had thicker myelinated axons than children, justifying the claim that myelination increases with age. However, it was noticed that children with ASD were born with a lower density of axons, suggesting that the pathology appears early. Therefore, there is a downward trend in axon thickness during the development of the disease. Corroborating this, in relation to the spacing between neurons, there was an increase in free space, suggesting that there was an increase in unmyelinated axons, due to the high expression of the axonal growth protein present in ASD, which is antagonistic to the expression of myelin proteins. As for the grey matter, a higher than normal metabolic rate and volume was observed, which interferes with the organization of synapses and makes the functions of the ACC more unstable (MEHMET HAZNEDAR M. el al 2018).

Joining the above study, HAU et al (2019) analyzed the U-shaped fiber system using probabilistic tractography in typical individuals and those with autism spectrum disorder. The cingulum contains a variety of white fibers exiting and entering its structure, dividing into different subsets that perform different functions, with the U-shaped cingulate fibers connecting the cingulate cortex with its adjacent areas. Analyzing 102 children with ASD and 77 with typical development between the ages of 7 and 18, they found that there is an alteration in the microstructure of the cingulum in ASD, together with an alteration of its own in the U fibers of the anterior cingulate cortex and macrostructurally these alterations are related to other pathologies. Demyelination was found, mainly in the left hemisphere, in addition to an asymmetry between the hemispheres, even with an age-related decrease in both parts, accompanied by a decline in fiber volume compared to typical children.

Some articles have tried to tie everything together by explaining the pathophysiology of the disorder. SCIARA et al (2020) analyzed pro-inflammatory and anti-inflammatory genes in patients with ASD and those with typical development. To do this, they selected post-mortem brain tissues from these two classes, sectioned into fixed thicknesses of gray and white matter. They selected the chains responsible for gene expression and the inflammation markers responsible for dendritic plasticity. They found that mechanisms that trigger neuroinflammation increase the development of this disorder. The result was that a high number of genes in the white matter of the anterior cingulate cortex tissue of individuals with this pathology generates an imbalance that ensures impaired neuronal communication due to altered synaptic plasticity. Other articles have linked the anatomical connectivity of the anterior cingulate cortex with adjacent areas in individuals with ASD to explain the symptomatic pathophysiology of this disorder (ANAGNOSTOU E. et al, 2021).

With regard to pain-related sensory abnormalities, greater activation of the rostral and dorsal ACC was observed during the anticipation of stimulation, but not during the application of stimulation and concluded that people with ASD have an aberrantly higher level of sensitivity to nearby aversive stimuli, which may reflect an abnormal attentional orientation towards nociceptive signals (ANAGNOSTOU E., et al 2018).

SIDOROV et al (2020) showed a relationship between the ACC and visual stimuli, proving this through a study of mice with Algeman (a neurodevelopmental disorder similar to autism). This study showed that ACC activity is visually driven and depends on the strength of the stimulus, the context and neural plasticity. The article concludes that abnormal sensory processing and differences in synaptic plasticity are common in autism, which justifies the interconnectivity of the two areas studied. In addition, it was found that visual stimuli directly interfere with social cognition, since patients with their eyes closed showed local overconnectivity in ASD in the posterior cingulate gyrus. In the eyes-open tests, there was local underconnectivity in the posterior visual regions and in the region of the cingulate gyrus, which negatively interferes with social cognition (MULLER, et al 2018). Get al (2020) and Trontel HG, el al (2018) assessed that altered connectivity changes the severity of communication in autistic children, i.e. children with underconnectivity between areas are classified as severely autistic.

In addition to this process, autistic children have decreased variability in sensory motor regions (pre- and post-central gyrus), which is why there are aberrant motor behaviors in this disorder, such as deficiencies in coordination, hyper- and hyposensitivity (MARSH R. 2019). YAN et al (2019) analyzed mechanisms

of aggression and social behavior, based on the distribution of parvalbumin and somatostatin interneurons. Taking into account that aggression is part of behaviors necessary for survival, through inhibitory mechanisms, it can be seen that if these fail, the individual loses their adaptive function, something related to autism, which is often accompanied by aggressive mechanisms. The experimental study with BALDB/cj mice (mouse model with aggressive behavior) and BALB control mice (non-aggressive strain) phenotyped for social behavior and aggression, were tested through a social interaction test, followed by the removal of the brain post-mortem, to histologically study the change in the level of interneurons, as well as the volume of the areas studied. BALDB/cJ mice were found to have a decreased concentration of these interneurons, causing a lack of sociability and aggressive behavior in the ACC and MCC, respectively.

Self-touch was also found to be related to deactivation in the insula, anterior cingulate cortex, superior temporal gyrus, amygdala, parahippocampal gyrus and prefrontal areas, common in autism spectrum disorder, in contrast to the hyperactivation of these areas to touch. This explains why people with autism, schizophrenia and emotionally unstable personality disorder have an aversion to social touch (OLAUSSON H, 2019).

The ACC is also related to the prefrontal cortex, ensuring, according to Salehinejad et al (2021), cognitive processes responsible for maintaining object-oriented goals. It has been observed that connectivity between frontoparietal attention networks is weaker (Satterthwaite TD. El al, 2019; Wenderoth N, 2018). In addition, Lau et al (2020) used a literature review of articles with experimental data obtained through functional magnetic resonance imaging, and concluded that the interaction of the two anatomical areas reaches a developmental peak in children, demonstrating that the initial connectivity failure had a significant impact at subsequent ages. This was proven in the analysis of children with ASD who showed functional hypoconnectivity and resulted in the typical characteristics of this disorder: cognitive inflexibility, lack of empathy and moral judgment.

Salehinejad et al (2021) using the same method of analysis, functional magnetic resonance imaging, observed that in autism there were abnormalities of the prefrontal-cingulate networks bringing deficits in behavioral reciprocity and social skills. The pathophysiological explanation of this process was studied by Trutzer et al (2019) through histological analysis of the prefrontal cortex and ACC of rhesus monkeys with typical autism compared to the brains of neurotypical individuals. This study concluded that in normal development there is an increase in myelinated axons from childhood to adulthood, decreasing the density of neurons, as well as inhibitory interneurons. With regard to the size of the myelinated neurons, it has been observed that at the beginning of life there is a greater quantity of fine (long-range) axons, with the proportion decreasing relatively with age and the density increasing through myelination. In autism, this network is disorganized, gradually decreasing the myelination of axons with age, suggesting an interruption in the maturation of neural tissue, together with a decrease in the presentation of inhibitory neurons (MIVAHARA M, el al. 2018). Therefore, it can be concluded that the activities guided by the prefrontal cortex related to the ACC have a flaw in individuals with ASD, guaranteeing the symptomatology of this disorder.

Another important study was the search for intrinsic relationships between the anterior cingulate cortex, responsible for empathy, and the posterior cingulate cortex, responsible for cognition, through the concentration of neurotransmitters with the aid of multiple neuroimages, analyzed in typical individuals and compared with children with ASD

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(ARIOLI et al, 2021). Firstly, using neuroimaging, You et al (2021), using the magneto encephalography approach in these restricted anatomical areas, observed that there are theta wave oscillations during the execution of various activities, indicating that there was a compensatory response of inefficient lexical semantic recovery in other anatomical areas, that is, due to flaws in the language development of individuals with ASD, they try to compensate with a greater activation of the ACC to try to make a cognitive control and selection of responses in complex social situations, and this increase indicates a demanding pattern of this anatomical area and indicate an atypical development in language.

Finally, Barlotti et al (2020) and Odriozola et al (2019), sought a relationship between the amygdala and the dorsal and ventral ACC from different perspectives, the first studied the relationship between anxiety and ASD, since according to the author it would be necessary to investigate neurophysiological processes, anxiety as a comorbidity, in order to analyze the neurobiological heterogeneity of autism, while the second related only autism spectrum disorder with socioemotional processing. According to Barlotti et al (2020), 232 participants were analyzed and divided into 3 different groups: ASD + anxiety, only ASD and typical development, the results were a decrease in connectivity in the dorsal areas studied related to emotional regulation in individuals who presented with comorbidity, and no change in those who presented only ASD, but no significant change in the ventral area. It is concluded that clinical anxiety in ASD may predominantly involve the disruption of amygdala connections with the dorsal ACC/PFC that are involved in emotion monitoring and appraisal functions. In contrast, Odriozola et al (2019) observed functional connectivity at rest in 58 individuals with typical development and 53 individuals with ASD, through the analysis of a resting-state functional magnetic resonance imaging, a hypoconnectivity between the anatomical areas observed was noticed, and this study took age into account, since in children and adolescents this connection is more pronounced than in adults.

In relation to the quality of synapses between adjacent areas, many studies have analyzed the neurotransmitters responsible for ASD. Jimenez et al (2021), focused their assessment on *N* -acetyl-aspartate (NAA), a neurotransmitter that is very abundant in the Central Nervous System and modulates the functioning of synapses related to attention and memory, as well as providing a reduction in the release of glutamate. According to this study, it was observed that the metabolism affected by the decrease in NAA and the increase in glutamate is generated mainly by mitochondrial dysfunction combined with lactic acidosis and reduced glucose utilization by the brain, as well as alterations in bioenergetic cycles. This process causes a reduction in protein expression in the brains of autistic patients, thus causing neuronal degradation and a delay in sending information, with a clinical response of socio-behavioral deficits, corroborating the central hypothesis of this research. With transcranial direct current stimulation (tDCS) treatment, there is a considerable increase in some metabolites (N-acetylaspartate/creatine, myo-inositol/creatine and decreased choline concentration), which generates a decrease in the severity of ASD symptoms, as it affects the neural activity of glial cells (PHUTTHARAK W. et al, 2020). Puts naj (2021) analyzed that the thalamus has less Glx (glutamate + glutamine) than the ACC, negatively affecting the maturation of synapses throughout life, in addition it is possible to observe that there is a lack of synaptic cell adhesion molecules in the ACC, causing alterations in social affiliation behaviors.

In this regard, Blatt GJ, (2019) discussed the density of serotonin receptors in the brains of autistic people. It was observed that there is a decrease in these receptors in the anterior cingulate cortex with age, while in people who do not have this disease there is an increase in these receptors with advancing age. Still on the influences that neurons can suffer, this article comments on the influence of intranasal oxytocin, which increased subjective ratings of pleasure from manual massage, as there were repercussions on neural responses in key regions involved in reward (orbitofrontal cortex, dorsal striatum and ventral tegmental area), social cognition (superior temporal sulcus and inferior parietal lobule), emotion and salience (amygdala and anterior cingulate and insula) and default mode networks (medial prefrontal cortex, parahippocampal gyrus, posterior cingulate and precuneus), as well as a range of sensory and motor functions. The combination of these two actions has therapeutic potential for autism (Zhang Q, et al., 2020).

Therefore, understanding how ASD genetically and pathophysiologically modifies the anterior cingulate cortex, many studies have sought ways to reverse the expression of this disorder early on, and to find alternatives for its treatment. **Murphy CM, et al., 2019** linked genetics to cortical volume changes through 22q11.2 Deletion Syndrome (22q11.2DS), which has different clinical phenotypes resulting from different forms of neuroanatomical presentation. The study **found a significant decrease in volume in the parietotemporal and cingulate regions**, an increase in volume in the bilateral insula and a significant reduction in AS in the bilateral dorsolateral-prefrontal-frontal cortices (DLPFC). The search for early microdeletions can predict clinical outcome, even before the first symptoms of autism or another clinical condition resulting from this structural abnormality. Alderman C. et al (2018) sought to understand the relationship between intranasal oxytocin and neural circuitry by modulating the functional output of the mesocorticolimbic dopamine system that processes rewards. The study states that the administration of intranasal oxytocin would result in greater activation and connectivity in the mesocorticolimbic regions of the brain, helping in the process of ASD, since it would change the atypical connectivity that autism has between these areas.

Among the selected articles where the descriptors: anterior cingulate cortex and autism were found, some did not establish a relationship between this anatomical area and the specified disorder. Some articles related schizophrenia instead of ASD in the analysis of results, others did not use the ACC as an area of focus, even considering ASD as the key disorder.

The article by TAYLOR SF et al (2019), analyzed people suffering from schizophrenia, reporting that this disorder exhibits greater sensitivity to stress and negative affect, which was named fragile brain. Thus, he experimentally analyzed the alteration of GABA function in parvalbumin interneurons, since this alteration has been analyzed in other disorders such as ASD. In addition, KIM et al (2021), Turner JÁ et al (2020) and Dell'Acqua F, et al, 2018 also analyzed schizophrenia as a key pathology, reporting that mice with deletion of the protein, IRSp53 and PSD-95 are expressed in various regions of the brain directed to post-synaptic structures in excitatory neurons of the anterior cingulate cortex, decreased the relationship with the dorsal medial thalamus, related to memory and cognition, presenting a pre-pulse inhibition that is considered an endophenotype of this disorder.

TAYLOR SC. Et al (2020), analyzed a deregulation of signals between neurons, mainly involving neurexins and neuroligins, which are related to scaffolding proteins:

SHANKs. Through a literature review, this study looked at how sCAMs (transmembrane proteins that help the synapse), relate to affiliation behaviors in key areas of the nervous system, that is, they relate to positive interpersonal interests, establishing the engagement of relationships, since the disruption of this process leads to ASD. It was observed that the mutation in genes that code for sCAMs alters synaptic maturation, leading to an imbalance in the medial prefrontal cortex (mPFC), basolateral amygdala (BLA), hippocampus and ventral tegmental area (VTA), not representing any area of study in this work, so it was excluded from the analysis.

GUO et al (2019) analyzed connectivity patterns of the right anterior insula (Rai) with the posterior cingulate cortex (PCA) and the ventral medial prefrontal cortex in individuals with ASD, compared to a control group using functional magnetic resonance imaging data. The anterior insula is the main region of the brain for interoceptive processing, and this area establishes connections that ensure brain function. When altered, it causes prominent social impairment, a pathology present in autism. The study found that standard individuals presented highly flexible dynamic functional connectivity, managing to adapt depending on the space, unlike individuals with ASD who presented abnormal variability in functional architecture, but were excluded from the analysis due to not presenting ACC.

BADURA et al (2018), highlighted the importance of the posterior cerebellum in delimiting and shaping behavioral development, through cerebellar microzones that contain stereotyped and repetitive circuits. This research does not focus on the anatomical area of interest in our study, only showing a brief relationship of lobe VI of the cerebellum that is coactivated with the cingulate cortex, being indicated as an associative area.

Mostofsky SH (2021) observed that the inferior parietal lobe makes connections with various regions of the brain, which makes socio-communicative skills possible; however, the study did not focus on ACC. In addition, Vinette S (2019) also did not address the area studied, but only showed the differences in learning in patients with and without ASD, in which patients with ASD were more flexible when making a choice, which differs from the others studied, and this was linked to the ventromedial prefrontal cortex. Dobbyn A, Li Q, et al, 2019, Keshavan MS, et al, 2020, Jao Keehn RJ, et al, 2019 and Cascio CJ, 2018 also did not relate the ACC in the study in question.

According to DECETY et al (2021), empathy involves a set of neural networks involved in social interaction and positive social relationships. Socialization difficulties are visible in ASD, and this study only analyzed in a practical way the way in which children relate to each other. In addition, SAKAGUCHI et al (2018) only related alcohol consumption with increased affective empathy, and both did not relate the anatomical area targeted by our work.

FINAL CONSIDERATIONS

Autism Spectrum Disorder is a highly underdiagnosed public health problem, which hinders effective therapeutic actions to control it. Its broad symptomatology makes it possible to create a network of autistic people with different degrees of evolution and clinical presentation, making diagnosis even more difficult. Therefore, several studies have tried to find anatomical areas that are closely related to this disorder, in order to create therapeutic possibilities for reducing symptomatological damage. The present study therefore analyzed the anterior cingulate cortex, since its neural command is directed towards the symptoms present in ASD.

From a detailed anatomical analysis of this cortex, it was noticed that, as it is responsible for social relationships, alterations were found in the amount of neurotransmitters, anatomical differences and unstable connections, facts that contribute to altered functional execution. In addition, as this is an epigenetic alteration, this literature review demonstrated the close relationship between this disorder and genetics and its involvement with various genes that alter the formation and development of the cerebral cortex, as well as the environment that influences the individual from birth.

Due to the scarcity of this study on Brazilian platforms, this topic is still little discussed, which makes this work even more important. Therefore, understanding the intrinsic relationship between specific anatomical areas such as the anterior cingulate cortex and ASD will help to specify areas that should be the target of treatment, not just medication, but also techniques that help to develop and direct neural impulses in this region.

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