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REVIEW

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Genetic polymorphism and neuroanatomical changes in schizophrenia

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Abstract

The article is a review of the latest meta-analyses regarding the genetic spectrum in schizophrenia, discussing the risks given by the disrupted-in-schizophrenia 1 (*DISC1*), catechol-O-methyltransferase (*COMT*), monoamine oxidases-A/B (*MAO-A/B*), glutamic acid decarboxylase 67 (*GAD67*) and *neuregulin 1* (*NRG1*) genes, and dysbindin-1 protein. The *DISC1* polymorphism significantly increases the risk of schizophrenia, as well injuries from the prefrontal cortex that affect connectivity. NRG1 is one of the most important proteins involved. Its polymorphism is associated with the reduction of areas in the *corpus callosum*, right uncinate, inferior lateral fronto-occipital fascicle, right external capsule, fornix, right optic tract, gyrus. *NRG1* and the ErbB4 receptor (tyrosine kinase receptor) are closely related to the *N*-methyl-D-aspartate receptor (NMDAR) (glutamate receptor). *COMT* is located on chromosome 22 and together with interleukin-10 (IL-10) have an anti-inflammatory and immunosuppressive function that influences the dopaminergic system. *MAO* gene methylation has been associated with mental disorders. *MAO-A* is a risk gene in the onset of schizophrenia, more precisely a certain type of single-nucleotide polymorphism (SNP), at the gene level, is associated with schizophrenia. In schizophrenia, we find deficits of the γ-aminobutyric acid (GABA)ergic neurotransmitter, the dysfunctions being found predominantly at the level of the *substantia nigra*. In schizophrenia, missing an allele at *GAD67*, caused by a SNP, has been correlated with decreases in parvalbumin (PV), somatostatin receptor (SSR), and GAD ribonucleic acid (RNA). Resulting in the inability to mature PV and SSR neurons, which has been associated with hyperactivity.

Keywords: schizophrenia, genetic inheritance, gene expression, neurobiology.

Introduction

Schizophrenia is a severe psychiatric disorder that is considered a major health problem. It affects approx. 1% of the globe's population, but this percentage could be much higher, because in underdeveloped countries not all data can be recorded statistically. Its widespread, global prevalence propels it to the top of the list of disabling disorders. Most commonly, psychosis begins between the ages of 15 and 35, but in some rare cases, it can begin both before the age of adolescence and after the age of 40.

The etiology remains unknown for the time being. There is a lot of research that implicates the genetic factor in the development of schizophrenia. Also, an impressive number of more than 260 genes [1] with potential risk in triggering schizophrenia [2] have been associated with the disorder. Genetic susceptibility plays an important role in the pathogenesis of psychosis. This can lead to deficient neural migration during intrauterine development or during extrauterine neurodevelopment. The genetic elements can be supplemented in the pathogenic process by certain external factors from the environment in which the individual develops.

Schizophrenia is a hypercomplex disorder in which a multitude of brain abnormalities are catalyzed. They produce, in some situations, irreversible effects that affect the person on all levels of functioning. The prognosis for this disorder is, most of the time, negative. Responsible for this severe projection is the progressive evolution that leads the patient to a severe state of disorganization. The symptomatology of schizophrenia is a complex one that includes positive (hallucinations, delusional ideas, etc.), negative (apathy, anhedonia, etc.) and cognitive (attention deficit, memory impairment, etc.) symptoms.

The onset of psychosis is sudden or insidious and puts an end to the social life the person enjoyed up to that point. Diagnosed people are affected socially and economically, due to the inability to work. The same goes for self-care behavior. In many cases, the patients remain in the care of the family or become institutionalized. This aspect contributes to affecting the quality of life (QoL), both for those diagnosed and for their families.

Epidemiology

The incidence is 0.17–0.54 per thousand people, prevalence is approximately 4.6 per thousand people, morbid risk cca. 1%. Mortality is 1.6 times higher than the general population (the most common causes being associated with cardiovascular pathology and suicide).

Pathogenesis of schizophrenia

Genetics

The genetic basis of schizophrenia is certified by

numerous research in the field. The high incidence among families, in which one parent was diagnosed with schizophrenia, drew attention for the first time to the possibility of hereditary transmission. Pedigree studies have highlighted the link between genetics and schizophrenia [3].

Genetic influence has benefited, in recent decades, from increased attention. But research has been quite limited, mainly due to the lack of adequate research means and tools. The interest shown in this field has increased a lot in recent years thanks to the advances in modern technology. As proof, we currently benefit from a very large number of studies, which can be accessed by researchers around the world, as is the case with genome-wide association studies (GWAS). Thus, complementary research can be joined, correlated, and interpreted that complements the knowledge we have about how genes influence overall functioning. Therefore, three polygenic models of transmission have been proposed, as follows: multifactorial model with threshold effect – schizophrenia would be transmitted by a few genes, each with a moderate effect, or by many genes, each with a weak effect; mixed model – transmission would be a combination of the effects of one major gene and several minor genes; the anticipatory model – it is based on certain dynamic mutations, which determine the early age of onset and the progressive accentuation of the severity of the symptoms, over the generations.

Genes represent a specific segment of the deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) molecule, which deals with the transmission of hereditary genetic information (traits and characteristics). Regarding the pathology, in the case of schizophrenia spectrum disorder, the genes undergo certain changes in function, caused by the occurrence of mutations or single-nucleotide polymorphisms (SNPs).

From the information we have so far, and from the proposed polygenetic models, we can say that a single gene cannot cause psychosis. Even though, in some situations, its variations can significantly influence homeostasis. The gene thus affected may, however, determine some susceptibility to the disorder. The pathogenesis of schizophrenia is a hypercomplex process, in which several variables are involved. Up to now, no single cause could be identified, leading to the onset of schizophrenia. Rather, this is the action of a complex of factors.

As we mentioned earlier, collaborations between researchers around the world, to better understand the human genome, have been materialized through a method that is extremely useful today, which is called GWAS [3–5]. Through this approach, gene variations can be tracked and identified, especially where there is a risk factor, or even where the disorder has already started. GWAS is extremely important in observing small variations, such as SNPs. With the help of GWAS, a series of mutations and polymorphisms that cause alterations in gene expression have been identified. Especially those that threaten the homeostasis of general functions. Studies [1] have shown that SNPs create different variants that are found in risk genes. Recently, the number of candidate genes for schizophrenia, identified through collective research, has increased significantly.

In the following lines, we will focus our attention on the most recent studies, which include the last five years of activity in researching the pathogenesis of schizophrenia.

The most popular risk genes in schizophrenia are disrupted-in-schizophrenia 1 (*DISC1*), catechol-O-methyl transferase (*COMT*), monoamine oxidases-A/B (*MAO-A/B*), glutamic acid decarboxylase 67 (*GAD67*), *dysbindin-1*, and neuregulin 1 (*NRG1*). This "title" is also given by early identification, some of which were discovered 20 years ago. Currently, the number of genes involved in schizophrenia has exceeded 200. How their variations appear, and function is not fully understood. As we will note, some of the candidate genes for schizophrenia have an important role in neurodevelopment. Although this kind of information was not known in the early days of psychiatry, autism, one of the most widespread neurodevelopmental disorders in children, was considered a form of juvenile schizophrenia. Recent studies show us that there is still a close structural connection between the two, but it is not significant to consider that they belong to the same clinical picture.

DISC1 is one of the most important candidate genes for schizophrenia. It (still) holds the "title" of the most researched gene in schizophrenia, being on the podium alongside the *COMT* and *NRG1* genes. It was discovered 20 years ago, and research [6] found that *DISC1* dysfunction is a predisposing factor, not only for schizophrenia but also for some psychiatric disorders (schizophrenia, bipolar disorder, depression, etc.). DISC1 is a protein that performs many functions, including neuronal migration, intracellular transport, synaptic maintenance, and stabilization, etc. [7]. Given the gene's involvement in neuroplasticity, numerous studies [8–12] have discussed the possibility that some of the *DISC1* polymorphisms increase the risk of developing schizophrenia. Following the dopaminergic hypothesis, which we will discuss a little later, the question of the extent to which *DISC1* expression impacts the neurotransmitter has been raised. Thus, statistical data were correlated, from research involving gene variations, but in which there were also altered dopaminergic circuits. The general conclusion was that *DISC1* has an influence on dopaminergic pathways [13, 14].

Another finding [15] shows that patients with schizophrenia have a low expression of *DISC1* gene messenger RNA (mRNA) compared to clinically healthy individuals. Very low mRNA levels were found in patients who had developed severe symptoms. Thus, abnormal gene expression could be directly associated with severe symptomatology, both positive and negative. *DISC1* is not only affected by polymorphisms, but the pathogenic risk also appears in the case of certain mutations discovered at the level of this gene [16–18]. Some of these may affect the functioning of the prefrontal cortex (PFC) [19] which will generate, in turn, deficits of executive functions. The damage to the PFC also has a severe impact on the social network in the human brain, and the major behavioral deficit, which this change causes, is the avoidance of social interactions and the tendency towards isolation [20–22], a characteristic element for patients with schizophrenia.

NRG1 is one of the most important proteins for the variety of functions in which it is involved. Among them are the growth and development of the epidermis, it is essential for the development of the nervous system (synaptic plasticity), it helps the functioning of the heart, etc. Gene variations are involved in several severe pathologies, such as cancer, schizophrenia, bipolar disorder, etc. It was first

associated with schizophrenia by Stefansson *et al.* [23]. Because *NRG1* plays a role in synaptic development, polymorphisms at its level have been associated with low levels of white matter in the area of the *corpus callosum*, right uncinate, inferior lateral fronto-occipital fascicle, right external capsule, fornix, right optic tract, gyrus. These structural abnormalities create imbalances found in disorders, such as anxiety, depression, and executive function deficits [24]. NRG1 and the ErbB4 receptor (tyrosine kinase receptor) are closely related to the *N*-methyl-D-aspartate receptor (NMDAR) (glutamate receptor). Receptor that, in healthy patients, has a higher density in hippocampus and cerebral cortex. In patients with schizophrenia, a decrease in the intensity of the function of NMDARs (under the influence of *NRG1*) [25] was observed, in those areas the density of the white matter was affected by the aberrant expression of *NRG1*.

Cortical disinhibition is a common element in several psychiatric disorders, including schizophrenia, autism, or intellectual disabilities. *NRG1* is involved in both excitatory and inhibitory function of neurons [26]. The inhibitory capacity of the cortical circuit appears to be obstructed by *NRG1* [27]. The study of the post-mortem brain [28] highlighted an alteration of circuits with an inhibitory role also at the level of the cerebral cortex. Thus, there are deficits in cortical interneuronal function caused by an overexpression of the *NRG1* gene in γ-aminobutyric acid (GABA)ergic interneurons (which have the role of regulating the function of cortical circuits). Deficits in cortical functioning cause psychobehavioral changes specific to psychosis. These include cognitive, social (interaction) and sensory-motor impairments [29].

A recent study [30] brings into discussion, for the first time, the visual disorders determined, in schizophrenia, by the aberrant expression of *NRG1*. The alterations discovered, through the electroretinography technique, are in the form of early degenerations in the retina. It is interesting to investigate, in future studies, the extent to which the damage to the retinal structure, due to *NRG1* expression, is present only in the case of schizophrenia, or there is a link between retinal pathologies and polymorphisms or mutations at the *NRG1* level.

COMT is responsible for controlling the synaptic transmission of dopamine (DA), catalyzing the degradation of the chemical mediator in the presynaptic space. *COMT* gene is located in chromosome 22 and encodes the enzyme of the same name. Both COMT and interleukin-10 (IL-10), which is an anti-inflammatory and immunosuppressive enzyme, have an important role in the dopaminergic system and the inflammatory response. A study [31], carried out in 2020, highlighted, for the first time, the close connection between COMT and IL-10. Both were associated with cognitive dysfunctions.

Another relationship was discovered between *COMT* and *MAO-B* [32], in terms of negative symptoms, especially anhedonia, caused by decreased DA levels. In this study, a gender-specific difference in affect was determined. Thus, women experienced a severe increase in the intensity of negative symptomatology associated with the *COMT* gene, and men experienced an increase in symptomatology attributed to the *MAO-B* gene. The gene polymorphism leads to accelerated DA degradation and impaired neurotransmission.

Resistance to antipsychotic treatment has been attributed to certain polymorphisms occurring in the *COMT* gene and the interaction with *MAO* [1]. The variations are associated with a drug-induced hypersensitivity to DA, which will not be degraded, thus generating excess DA receptors. In this case, treatment with classical antipsychotics will not achieve its goal.

Monoamine oxidases (MAOs) are a family of enzymes whose purpose is to break down monoamines in the body [33]. Some of these are neurotransmitters, and when their function is impaired, disturbances occur that give rise to psychiatric symptoms. One of the roles of MAO in the body is to break down the monoamines in the food we eat.

In humans, two categories are found: MAO-A and MAO-B. Both variants are found both in and outside the central nervous system (CNS), specifically in neurons, glial cells, and the spinal cord. MAO-A is found in the lungs, liver, gastrointestinal tract, and placenta. MAO-B is found in platelets.

One of the directions drawn by modern genetics is the study of DNA methylation, as a possible influencing factor in the occurrence of mental disorders. This process is of crucial importance as it dictates where and when gene expression will occur. *MAO* gene methylation has been associated with mental disorders [34]. This direction of *MAO* methylation needs to be better understood. It could also have a positive impact on the development of new therapeutic approaches.

MAO-A is a risk gene in the onset of schizophrenia, more precisely a certain type of SNP, at the gene level, is associated with schizophrenia [35, 36]. As we have already stated, one of the roles of *MAO-A* within the CNS is to break down both DA and serotonin (5-hydroxytryptamine, 5-HT). When the polymorphism sets in, gene expression is affected, and DA breakdown is reduced. Thus, monoamine levels increase. This dysregulation was associated with positive symptomatology in men [1, 37].

Accelerated DA degradation, caused by the *MAO-B*, has been associated with negative symptomatology and is much more common in women diagnosed with schizophrenia [32].

Glutamate decarboxylase (*GAD*) is another risk gene associated with schizophrenia. Structurally, it is an enzyme that catalyzes the decarboxylation of glutamate into GABA and carbon dioxide. *GAD* occurs in the body as the *GAD1* and *GAD2* genes. Both can be detected in the brain, where GABA acts as a neurotransmitter. However, *GAD2* can also be located in the pancreas.

GAD67 is an isozyme encoded by *GAD1* and *GAD2*, involved in the synthesis of GABA and is a target of antigen tests for the determination of diabetes mellitus. The connection between *GAD* and diabetes makes a significant part of patients with schizophrenia have a predisposition to this disease, especially to type 2 diabetes [38]. 67 kDa isoenzyme of brain GAD generates dysfunctions of the GABAergic system by inhibiting dopaminergic neurons (D2) [1]. In schizophrenia, deficits in the GABAergic neurotransmission system can be found in several areas of the brain. One of the recent research projects [39] raises the issue of DA hyperactivity at the level of the midbrain. This problem is caused by dysfunctions of the GABAergic system in the *substantia nigra*.

The midbrain is an important area of the brain that has functions, such as response control, eye movement, pupil dilation, regulation of muscle movement, and hearing. High levels of DA in this region, caused by gene expression, may be associated with auditory hallucinations. The explanation resides in low densities of parvalbumin (PV)-immunoreactive interneurons and surrounding perineuronal nets within the inferior colliculus [40].

Alterations in the expression of the *GAD* gene in regions, such as the superior temporal gyrus, the dorsolateral thalamus and the medial dorsal nucleus, the dentate gyrus in the hippocampus were affected by severe dysfunctions of the GABAergic system, in the case of patients diagnosed with paranoid schizophrenia [41, 42].

In schizophrenia, missing an allele at *GAD67*, caused by a SNP, has been correlated with decreases in PV, somatostatin receptor (SSR), and GAD RNA, resulting in the inability to mature PV and SSR neurons, which has been associated with hyperactivity. The same problem occurs in attention deficit hyperactivity disorder (ADHD) and Tourette syndrome [43].

Recent studies in mice have demonstrated that reducing the expression of *GAD67*, up to its definitive blocking, causes emotional abnormalities and alters conditioned fear behavior. Thus, the fear of certain objects or certain contexts, which in the past represented a danger, disappears [44]. GABA synthesis, produced by *GAD67*, has an important role in the contextualization and differentiation of fear memory. This aspect may explain how schizophrenic patients venture into all kinds of dangerous situations. Thus, new insights are emerging into how the neurobiological mechanism that influences emotions works [45].

The role of dystrobrevin-binding protein 1 (*DTNBP1*) gene in the brain is not fully understood, and from what we know so far, one of its tasks is to modulate the functioning of the prefrontal area of the brain. *DTNBP1* SNPs and mutations [46] propel the gene as a candidate for schizophrenia.

Dysbindin-1 is a critically important protein encoded by *DTNBP1* that has implications in neuronal neurodevelopment and neuroplasticity. Its abnormal functioning has been linked to schizophrenia [47, 48]. Dysbindin-1 is abundant in the prefrontal area and hippocampus in clinically healthy individuals. But recent research has revealed low levels of protein and mRNA in these areas in patients with schizophrenia [49].

Older research [50–52] has shown that there is a significant reduction in dendritic branches in the dorsolateral PFC. But the molecular mechanism by which this abnormality occurred was not understood, nor was the influence it had on psychosis. Recent findings [53] state that dysbindin-1 expression has a role in the pathology of the dendritic tree in the dorsolateral PFC. Thus, we can better understand the molecular mechanism by which this abnormality occurs, in the case of schizophrenia and bipolar disorder.

DTNBP1, like the *NRG1* gene, has an impact on glutamate neurotransmission [54], a circuit affected in schizophrenia. The most recent research [55, 56] focuses on the low level of glutamate in the PFC, which occurs following a mutation that cancels dysbindin-1 function. Lack of the protein impairs GABAergic transmission in the PFC and hippocampus. Following this impairment, the subject's cognitive deficits will be severe. In addition to glutamate transmission, abrogation of dysbindin-1 functions acts as a chain reaction that also leads to impairment of copper transport [57–60]. Affecting the latter will generate a deficiency of this metal, crucial for cell homeostasis.

Lissencephaly 1 (*LIS1*) is one of the main genes associated with the onset of lissencephaly [61], also known as Miller–Dieker syndrome. This genetic condition is characterized by the abnormal migration of neurons in the brain during the intrauterine period and the absence of the *corpus callosum*, associated with severe mental retardation, heart disease and, in very rare cases, polydactyly. There are few associations of the gene variation with the onset of symptoms found in schizophrenia. Several research [62, 63] correlate the interaction of *LIS1* variations with those of *DISC1*, an interaction that leads to the cognitive impairment specific to psychosis.

The most recent study [61] raises some questions about how *LIS1* works on its own and shows that deletion of the first coding exon of the gene can produce cortical abnormalities, commonly seen in schizophrenia.

D-amino acid oxidase activator (*DAOA*) or *G72*, dubbed the "interaction partner" of *DAO*, which it regulates, also plays an important role in glutamatergic transmission and mitochondrial function [64]. Dysfunction of the *DAOA* gene is associated with alterations of the glutamatergic system, through the hypofunction of NMDAR [65]. This implies a high degree of susceptibility for schizophrenia and bipolar disorder [66].

DAOA has also been studied in interaction with other genes, a context in which it has been shown to have a significant impact in the development of schizophrenia. There is an association between *DISC1* and *DAOA*, which could be responsible for the early onset [67] of schizophrenia.

The same genes, but in the interplay of different variations, appear to affect visual learning in schizophrenia patients [68]. As in the case above, the interaction between *DAO*, *DAOA* and *NRG1* polymorphisms are charged with a significant role in the development of schizophrenia [69].

DAOA is considered a gene with a strong susceptibility factor in the development of schizophrenia [70], and when certain variations are in interaction with other genes, it can even determine the early onset of the disorder.

At least interesting is the approach to nicotine as an adjunct in the treatment of schizophrenia. The habit of smoking is quite common among patients diagnosed with schizophrenia, and several studies on mice [71] show us that this habit can even be one that can improve symptoms. Nicotine administration, in mice with variations of the *DAOA* gene, normalizes the dysregulation of the oxytocinergic system and modulates cognitive deficits. However, the possibility of this being a real help in the therapy of schizophrenia needs to be studied further [72].

Some of the studies dealing with schizophrenia have focused on other, less researched genes. Regulator of G-protein signaling 4 (RGS4) is an intracellular protein that has implications in pain and in the control of cardiac contraction.

A significant decrease in the expression of this gene was found in research [73] on post-mortem brains of patients diagnosed with schizophrenia. The findings suggested that

the gene might be considered a possible candidate for schizophrenia susceptibility. Recent studies [74, 75] do not integrate RGS4 among risk factor genes but indicate its importance in a complex biological mechanism underlying the risk of triggering the disorder.

RGS4 joins the "select club" of genes influencing glutamatergic system dysfunction [76]. A low expression of the gene was also observed in the PFC. The behavioral consequences of the dysfunction have been associated with stereotypies, impaired momentary response inhibition, behavioral inhibition, impaired working memory, and difficulties in social interaction.

Zinc finger DHHC-type palmitoyltransferase 8 (*ZHHC8*) is a protein-coding gene, one of the most little studied whose polymorphism may have an influence on cortical volume irregularities [77]. Disruption of *ZHHC8* gene expression, due to a mutation, can cause cognitive deficits associated with schizophrenia [78].

AKT has been known for 50 years and studied for its contribution in oncogenesis. Recent research [79] attempted to determine the link between two isoforms, specifically *AKT1* and *AKT3*, and psychiatric disorders. Mutations of *AKT1* [PKBα, Online Mendelian Inheritance in Man (OMIM): 164730] and *AKT3* (PKBγ, OMIM: 611223) present in patients with schizophrenia were thus discovered.

Studying variations in these isoforms is still in its infancy, so more research is needed. Inhibition of AKT expression in the CNS has been associated with psychiatric symptoms, such as insomnia or anxiety and depressive symptoms [80]. These symptoms are joined by the attention deficit found in schizophrenia [81]. It has also been established that *AKT1* has a role in modulating GABAergic function and $GABA_A$ receptors in the hippocampus, which can generate impaired cognitive functioning [82].

Zinc finger protein 804A (ZNF804A) is a "zinc finger" that performs vital functions for the body. Some of them regulate gene expression [83]. Protein is a transmission factor, it has an important role in the release of hormones and in the transit of nerve impulses, etc. Among many other functions, it also facilitates neurotransmission, and when it is not found in sufficient amounts in the brain, structural brain decline associated with cognitive decline can occur. *ZNF804A* has recently been cataloged, by means of GWASs, as a risk gene in schizophrenia [84], due to its importance in the regulation of *COMT* and serine protease 16 (*PRSS16*) gene expression [85]. The gene has also been associated with the ability to regulate DA levels, specifically, certain variations affect the ability to capture receptors [86, 87].

And the functioning of the PFC seems to suffer due to variations in the level of ZNF804A [88]. This time, because of the influence it has on COMT, it can generate the quantitative change in the volume of the gray matter, from the dorsolateral PFC.

GWAS is proving to be an extremely important tool in studying the action of gene variations. By this method it was observed that *ZNF804A* regulates the expression of a subset of genes involved in synaptic development and neurodevelopment [89–91]. The involvement of *ZNF804A* in neurodevelopment led to the association of the impact of polymorphisms on autism [92], but the results were inconclusive. The same variations, considered risk factors for schizophrenia, create susceptibility for mood disorders (depression and bipolar disorder) [93].

The multitude of functions and the importance it has in maintaining the balance of the whole organism, places the gene on the leading positions in the top of the risk factors in the onset of schizophrenia. Variations, caused by polymorphisms or mutations, can generate a domino effect that destabilizes the general functioning of individuals. The universe of action of *ZNF804A* has not yet been fully elucidated, and studies linking gene variations to schizophrenia are just beginning.

Because a disorder does not manifest itself in the same way, even in terms of biochemical processes, an alteration of the function of the glyoxalase 1 (*GLO1*) for some patients with schizophrenia. Aberrant gene expression can reduce enzyme activity in the brain. Thus, a significant reduction of vitamin B_6 in peripheral blood vessels was observed. However, this finding is recent, and how the brain of a schizophrenic is influenced by this deficit needs further analysis [94]. At a structural level, low levels of vitamin B_6 generate oxidative stress that ages nerve cells – an aspect that could explain how certain regions of the brain are aged at the onset of schizophrenia. Behaviorally, the deficit has been associated as a contributing factor to sensorimotor impairments, memory deficits, disinhibition of momentary impulse, and poor social interactions.

Continued genetic studies are particularly important and urgently needed. It is one of the ways that can answer the questions that still hover both about how homeostasis works and about the genesis of pathology. Technological advancement is a significant advantage that contributes greatly to the results and knowledge we have at the moment.

One of the most important, but also controversial, discoveries of our century is artificial intelligence. Its use in genetics contributes substantially to the understanding of a variety of biological mechanisms that occur at the micro- and macromolecular level. Also, imaging technology has advanced a lot, as has modern biotechnology that has managed to make possible processes that, until not long ago, belonged to the realm of the fantastic.

Fully understanding how genes express themselves or undergo certain variations is vital. This could generate new perspectives in the treatment of psychiatric disorders, but not only. The implications will be far-reaching. Important progress is already being made in this direction. As we know, work has been going on for several years to develop biotechnologies involving mRNA, which is used with very good results in anti-coronavirus disease 2019 (COVID-19) vaccines. This technology has shown promise against some types of cancer and against the human immunodeficiency virus (HIV).

The neurobiology of schizophrenia

As we have noted, genes influence the way the entire organism functions and develops. Certain variations of these pose a threat to the overall homeostasis. Changes occurring at the level of genes can generate major disturbances that exceed the threshold of normality. Schizophrenia is a multi-factorial disorder, in which many functional imbalances are associated, both in the brain and outside it. They can be caused, as we have noticed in the previous pages, by a mix of genes in relation to environmental factors or have

an organic cause. In psychosis, the entire anatomical-biological functioning of the brain is affected, and at its base is a hypercomplex mechanism in the understanding of which there are several gaps.

In the last decade, efforts have been made to establish certain biomarkers by which schizophrenia can be identified early, for the purpose of rapid intervention, before the onset. However, the complexity of the disorder makes this difficult [95], at least for the time being.

Although the pervasive mode of action of schizophrenia is not fully understood and we do not benefit from the help of biomarkers, in the early detection of the disorder there are some insights into how it works at the neurobiological level. In this continuum of attempts to understand the pathogenesis of schizophrenia, three hypotheses have been developed: the dopaminergic, the glutamatergic and the serotonergic hypothesis, which would be the basis of the pathogenic mechanism in schizophrenia. These hypotheses have been confirmed, in part, by recent genetic research. Functional imbalances at the level of the three chemical mediators have been demonstrated, but not separately. The quantitative imbalance of one neurotransmitter automatically influences the activity of other neurotransmitters.

Dopaminergic hypothesis

One of the most important neurobiological imbalances is that of dopaminergic pathways, which, in addition to their organic role, should ensure the maintenance and functioning of cognitive processes. In the case of schizophrenia, the ability to self-regulate is altered, and the dysfunctions of the processes of secretion and capture of chemical substances are more and more numerous. At least that is what the latest research tells us, which comes to complete a still incomplete clinical picture. Positive symptomatology (hallucinations and delusional ideation) from psychosis has been associated with out-of-control DA levels. Excess DA from the synapse is cleared and conducted by the DA transporter (DAT) to the vesicular monoamine transporter 2 (VMAT2). The process is continued to the synaptic vesicles, where it is stored. When this process is impaired, neurotransmitter imbalances occur. The abnormal flow of DA that remains outside the vesicles is directly proportional to the severity of the symptoms.

In the case of schizophrenia, dysfunctions of the dopaminergic system have been identified, consisting of high levels of the neurotransmitter, especially in the subcortical region. A high level of DA has been observed in synaptic regions in the striatum [96]. The latest meta-analysis [97] discusses the establishment of high levels of neuromelanin, resulting from increased DA fluxes, as a possible biomarker for schizophrenia.

At the structural level, all four circulation pathways of DA within the brain are affected in schizophrenia– mesolimbic pathway: from the ventral tegmental area (VTA) to the *nucleus accumbens* (part of the limbic system of the brain) – involved in the sensation of pleasure, delusions, hallucinations, or in the production of euphoria, in the case of drug abuse; the meso-cortical pathway: from the VTA, which sends its axon extensions to the PFC, having a role in mediating cognitive and affective symptoms in schizophrenia; the nigrostriatal pathway: from the *substantia nigra* to the basal nuclei, it is a part of the extrapyramidal nervous system that has a role in controlling movements; tubero-infundibular pathway: from the hypothalamus to the anterior pituitary gland and has a role in controlling prolactin secretion.

Aberrant gene expressions are directly responsible for DA modulation. But there are some gaps regarding the mechanism of operation and the effects that the imbalance of DA levels produces.

There are certain people whose symptoms, associated with high amounts of DA (as hypothesized), are resistant to inhibitory treatments. In these cases, symptoms persist even after inhibitory medication has been administered. There is research, as we showed in the previous subsection, that implicates certain variations of the *COMT* gene in resistance to treatment.

In addition to treatment-resistant patients, a very serious problem arises in patients who develop psychotic manifestations secondary to Parkinson's or Alzheimer's disorders. Medication that blocks the DA (D2) receptor from the mesolimbic system aggravates symptoms, such as hand tremors or stiffness of movements, in Parkinson's, and can cause death in Alzheimer's patients [98–100]. Thus, antipsychotics that target DA blockade do not work for all patients who develop specific symptomatology.

The Stahl glutamate hypothesis

The Stahl glutamate hypothesis [101] changes the perspective of a single mediator involved in schizophrenia. He discovers that alterations in glutamate levels in the PFC are the result of DA hyperactivity. Currently, there are a multitude of studies, including genetic research, indicating dysregulation of the glutamatergic system, especially NMDAR dysfunction [102]. Alteration of the glutamate pathway in the ventral striatum and VTA has been associated with the symptomatology of auditory hallucinations, especially those with a paranoid content [103, 104]. In general terms, excess glutamate in the cerebral cortex has been associated with hallucinations. Understanding how this circuit works and the role of the NMDAR gives us new insights into treatment-resistant patients.

The serotonin hypothesis

Serotonin functions in synaptic vesicles as a neurotransmitter and neurohormone. Associated functions include emotion regulation, learning, working memory, thinking, and certain motor processes. Dysfunction of serotonin pathways has been associated with psychiatric disorders. In schizophrenia, high levels of serotonin have been observed in areas of the anterior cingulate cortex and in the dorsolateral frontal lobe, being associated with the appearance of positive symptoms [105]. The serotonin hypothesis emerged after studies showed a decrease in hallucinatory behavior and a slowing of the progression of the disorder when drugs that blocked 5-HT_{2A} receptors were administered.

Excess levels of serotonin produce a series of chain effects and underlie the mechanism for activating glutamate release. This, once released in large quantities, led to the hyperactivation of dopaminergic pathways in the mesolimbic system [106]. We are practically witnessing a chain reaction, at the level of chemical mediators. This situation is the most eloquent to demonstrate the validity of the hypothesis that all neurotransmitters are interconnected.

In the past, starting from the research of amphetamines, which induced a state similar to schizophrenia, the first psychiatric treatments based on the dopaminergic hypothesis were created. They worked by blocking D2 receptors in the mesolimbic system pathways. The research was relevant at the time, and the treatments were effective (except for patients who had resistance to the active substance and those who developed severe side effects). High levels of DA were associated with severe positive symptoms, which were stopped by treatment. Some research, which we have discussed in previous pages, further links high DA levels to positive symptomatology. But the process by which these imbalances appear is much more complex.

The way gene variations are expressed and lead to fluctuations in neurotransmitter levels, along with the fact that some patients are resistant to treatment aimed at blocking a single neurotransmitter suggests that schizophrenia is a disorder whose mechanism involves the functioning of all neurotransmitters. The three pathways (DA, glutamate, and serotonin) are interconnected, and when one does not work at optimal parameters, chain reactions occur that, in certain cases, generate structural alterations (atrophy of some regions) and give rise to the specific symptoms of schizophrenia.

Brain structure in schizophrenia

Anatomical changes and their impact

Because we discussed the structural changes in the brain, we can say with certainty that any imbalance causes certain changes, and the aberrant way in which the neurobiological mechanisms work can influence the brain structure [107]. Brain shape is different in patients with schizophrenia. Imaging studies [108] revealed deformations of the hippocampus, amygdala, *nucleus accumbens* and thalamus, whose shape was convex, in people diagnosed with psychosis, and concave, in clinically healthy people. The *putamen* and *pallidum* also underwent a change in shape, becoming convex. Again, at the opposite pole are unaffected people, the shape being concave. Changes in appearance were also observed in the caudate nucleus. The same type of structural changes has been found in autism spectrum disorder (ASD). These changes are caused by reduced gray matter density in those areas.

The biopsychological phenomena that occur in the brain in schizophrenia influence the neurodevelopment of gray matter, both qualitatively and quantitatively. A reduction in the volume can also occur as a degenerative factor as we age and is part of the natural aging process. In schizophrenia spectrum disorder (Tay–Sachs disease – TSD), volume irregularities have been observed in certain brain regions. The change in volume is visible even in teenagers diagnosed with TSD. This abnormality has also been associated with premature aging of the brain. In both adolescents and adults, there is a low level of gray matter density in the area of action of the default mode network, whose function is strongly affected in psychiatric disorders. The same type of structural change is found in the activity area of the cortical network and in the salience network [109, 110]. Low density in different regions affects the connectivity of neural networks [111]. Volume differences also resulted in altered brain sizes in TSD patients.

An interesting finding has been made in people with schizophrenia who have not benefited from antipsychotic treatment for a long period of time. Thus, the degenerative reduction of gray matter, associated with the aging process, was found in all individuals without treatment. The severity of symptoms was directly proportional to the length of time the patient was off treatment [110]. Late diagnosis of the disorder is risky and brings with it structural degenerations that cause severe symptoms. This degenerative process can occur even in children and adolescents, the most affected areas of which are the PFC, the hippocampus, and the cerebellum [111–113].

Because the gray matter covers an important part of the brain and facilitates the functioning of the entire nervous system, it was and is an intensively researched structure. Shape oscillations attracted the most attention, so a decrease in volume was also observed in the area of cholinergic neurons, from the base of the striatum to the hypothalamus. This abnormality has been correlated with difficulties in maintaining sustained attention and difficulties in decision-making and processing [114]. And reaction times are strongly affected, because of these irregularities [115].

Differences in volume and structure were also found at the white matter, correlated with significant cortical deficits. Imaging research, based on the latest technologies, has revealed numerous white matter abnormalities [116, 117]. One of the novel findings of this research was the increase in the volume of extracellular water. The causes of these accumulations are not fully understood. One possibility could be brain inflammation [118].

White matter has a role in the development of parkinsonism in patients with schizophrenia, which involves motor slowness, rigidity, or tremors. This symptom appears because of the alteration of the structure of the matter and the poor connectivity between the regions of the orbito-frontal cortex, frontoparietal and the *striatum* [119, 120].

White matter damage has also been associated with positive symptoms in schizophrenia, particularly verbal hallucinations. Abnormalities encountered in the structure of the white matter at the level of the *corpus callosum*, *corona radiata*, superior frontal occipital bundle, fornix and terminations of the striatum can generate an aberrant connectivity between the frontotemporal region and the two cerebral hemispheres [121].

Another abnormality of the white matter microstructure was observed in the anterior cingulate cortex, the inferior parietal lobe, and the premotor cortex, where the formation called mirror neurons. Irregularities in the composition of white matter could also have an unwanted impact on negative symptoms, more precisely at the level of the patient's inability to feel intimacy (theory of mind) [122]. Damage to the microstructure of matter in the bilateral superior, uncinate fasciculus, cingulate and *corpus callosum* could be related to the appearance of negative symptoms, such as apathy and avolition [123]. Thus, we can state that differences in the structure of white matter can generate the appearance of both positive and negative symptoms [124].

To map how neurons mirror in psychosis, a lack of connections between V5 visual area and the temporal gyrus was analyzed [125]. This process leads to impaired perception, processing, and impaired imitation in patients with schizophrenia [126].

Resistance to treatment was also associated with damage to the microstructure, at the cortical and subcortical level, of the white matter [127]. This anomaly could be the result of altered mediator pathways.

There are, however, unknown matters when considering the factors that produce changes in white matter structure. The most obvious of these would be strokes. Another possibility has been attributed to blood pressure. Hypertension can cause, in the brain, microhemorrhages that can be associated with cognitive decline [128]. Atherosclerosis is also a possible factor that could damage the white matter structure [129]. Few studies consider stress as a factor in the deterioration of white matter structure. This, among many other functions, connects the limbic system with the prefrontal region, which has a role in regulating the stress response. The possibility that elevated levels of glucocorticoids, particularly cortisol, may affect white matter tissue should not be overlooked. In areas where high levels of cortisol were recorded, a deficit of white matter was also observed [130]. This perspective may draw new directions regarding the treatment of psychotic patients.

There is significant evidence regarding the functional connectivity of neural networks connecting brain regions in patients with schizophrenia. Research conducted with transcranial magnetic stimulation technology has demonstrated that there is a malfunction of cortical networks [131, 132] thus leading to severe cognitive dysfunction. The occurrence of these abnormalities is determined, most of the time, by the expression of genetic polymorphisms or mutations [133].

As for the subcortical structures, they are a group of neural formations that include diencephalon, the pituitary gland, the limbic structures, and the basal ganglia. They are structures with complex functions involving memory, emotions, and pleasure. It was found that patients with schizophrenia have a smaller volume of these areas, both compared to clinically healthy people and compared to patients diagnosed with other psychiatric disorders [134]. It functions as an information hub in the neural networks that interconnect different regions of the brain. It also plays an essential role in the pathophysiology and treatment of schizophrenia, being an area that performs a variety of functions. Among them we mention: the production of hormones and the synthesis of neurotransmitters.

In the following lines, we will detail the deficits that occur in the most important brain areas and the effects they have on behavior.

The thalamus

The thalamus is a part of the diencephalon affected in schizophrenia. Abnormalities of thalamo-cortical connectivity, implying disturbances in the functioning, on a large scale, of neural networks. They have a severe impact in the cognitive, social, and sensorimotor domains [135].

A recent and especially important discovery [136] is that of iron accumulation in the thalamic area. The discovery is significant, as it could serve as a biomarker for schizophrenia. The non-invasive possibility to measure the degree of metal accumulation in the thalamic region represents a considerable advantage.

Pituitary gland

Another volume irregularity was observed in the case of the pituitary gland: it has a smaller size in the case of patients with schizophrenia, an aspect that influences the ability to produce hormones. The structural change leads to dysregulation of hypothalamic–pituitary–adrenal function, and cortisol secretion will be altered. Measuring the concentration of cortisol in the hairs resulted in a very high concentration of the hormone. Secreted in large amounts, in the long term, it can have serious consequences on the individual's health [137]. The causes that determine the alteration of the volume of the pituitary gland are not very well understood. One of the factors that could influence the volume change of the gland is stress itself [138], and the most prone were the people who were sexually abused in childhood, or whose psychological traumas were of high intensity. The link between sexual abuse and schizophrenia has not been established by research (more studies are needed), but the stress of this trauma can have effects on both mental and physical health.

Limbic system – parts affected in schizophrenia

Hippocampus

As with the pituitary gland, the volume of the hippocampus is lower and normal functioning is affected [139]. In this case, there is no longer the influence of a direct external factor, but the structural change can be associated with neurodevelopment deficiency [140]. The changes lead to altered function, and the hippocampus is one of the parts of the limbic system that influences glutamatergic transmission, whose altered functioning is already a constant in schizophrenia [141].

Insula

Another region of the limbic system affected by schizophrenia is the *insula*, whose activity influences higher processes, such as abstract thinking or decision-making. It also participates in the following actions related to general functioning: taste and smell, influences heart rate and blood pressure, vestibular function, addiction, and by association with other regions of the brain, influences the integration of perceptual and emotional. It is also associated with empathy. In schizophrenia some of these functions are deficient. At the structural level, a reduction of gray matter was observed in the insula region, in the medial PFC [142].

The latest research also links this region to the fear response or persecutory ideation [143]. Imaging studies have shown, this time, the existence of hyperconnectivity between all regions associated with processing and modulating the fear response (insula, PFC, and bed nuclei of the *stria terminalis*), which, as noted, can cause paranoid ideation. But, paradoxically, the ability to anticipate danger is impaired, due to poor connectivity between other brain regions [144].

If we mentioned the fear response, then the amygdala could not escape unscathed either. For the first time, in 2021, research revealed patterns, at the level of the amygdala nuclei, associated with schizophrenia [145]. These can complete the series of changes in brain size that could be used to diagnose the disorder at an early stage.

Gyrus

The gyrus is also affected in neurodevelopment. Abnormal gray matter thinning has been observed in this region [146]. The anomaly was associated with severe

positive symptoms. Damage to the inferior frontal gyrus hinders the development of the ability to abstract in schizophrenia patients, especially the understanding of speeches and gestures that have a certain implication [147]. The same processing deficit is found in ASD. This area is also involved in the processing of spontaneous speech which in schizophrenia leads to a deficit in language processing [148].

Structural alterations are also found at the level of the anterior cingulate gyrus; it is involved in processing and cognitive and the cording of emotion-related behaviors [149].

Basal ganglia

Ganglia are a group of subcortical nuclei that are part of the CNS. They are connected to the cerebral cortex, brainstem, and thalamus. The composition of the basal ganglia consists of the striatum, dorsal (caudate nucleus and putamen) and ventral (*nucleus accumbens* and olfactory tubercle), globus, ventral *pallidum*, *substantia* and subthalamic nucleus. Some of their functions are impaired in schizophrenia due to aberrant interconnection [150]. So, affected people will have difficulties in the learning process, processing emotions, voluntary control of movements or even difficulties in eye movement, as we can see in certain cases of catatonia.

The *nucleus accumbens* is attached to the ventral *pallidum*, connecting the basal ganglia and the limbic system. Some of the behavioral functions it has been associated with are motivation and avoidance of risky situations. In schizophrenia, the neurobiological function is affected by the altered expression of the *DISC1* gene. This resulted in an inability to assess risk and lack of motivation for social interactions [151].

The corpus callosum

Another structure that is closely related to the limbic system is the *corpus callosum*. This structure is formed by nerve fibers that connect the cerebral hemispheres, thus realizing the connectivity between the two parts. Structural deficits in this area have been associated with chronic schizophrenia. It appears that the disorder itself is responsible for certain micro- and macrostructural abnormalities that occur in this area. Research [152] has shown that long-term treatment with risperidone has a positive effect on white matter volume in this region. The importance of the *corpus callosum* is abundantly clear, but there are many unknowns regarding the role of structural changes in psychosis. More research in this direction could solve certain questions related to the internal mechanisms of schizophrenia and autism [153].

Major regions involved in schizophrenia

Frontal lobe – prefrontal cortex

One of the major regions involved in schizophrenia, and which is closely related to the limbic system, as we could also observe from the trajectory of dopaminergic pathways, is the frontal lobe [154]. The most important part of the frontal lobe affected by schizophrenia is the PFC, an area highly interconnected with other regions through both cortical and subcortical connections. The PFC has been attributed to, among other things, executive functions, social behaviors, memory, and cognitive abilities.

Through neuroimaging research, dysfunctions have been observed in certain areas that make up the anatomical structure of the PFC, as follows:

▪ Dysfunction of the dorsolateral area of the PFC is a constant in patients with schizophrenia. This dysfunction is associated with cognitive deficits specific to the disorder [155], including working memory. The latter depends on pyramidal neurons, which serve as the primary excitatory units of the PFC [156]. This formation is indispensable for functioning, any element that disrupts pyramidal neurons has a negative impact on higher mental functions, or on behavioral control.

▪ There is a collective effort, by researchers around the world, to decode how schizophrenia infiltrates and becomes a disorder with a negative impact on the QoL of patients and their families. So, as we have noticed, we are trying to determine some biomarkers or some patterns (as also happens in the case of volume differences) through which early detection of psychosis is possible.

Another anomaly that could serve as a pattern in the early diagnosis of the disorder has been observed in both adolescents and adults with schizophrenia: a volume difference in the posterior region of the medial PFC that is larger, compared to the same region of clinically healthy individuals. Also, the visual cortex has a smaller size than in healthy people. One of the causes that could lead to such a difference in structure has been attributed to mitochondrial dysfunctions [157]. Such dysfunctions at the level of mitochondria produce, in turn, chain effects that influence DA, create dysfunctions of the glutamatergic circuit and lead to oxidative stress, which affects brain cells [158].

Interneurons, which connect different regions of the brain, were misdistributed during the extrauterine period, so that the perineuronal networks, in the PFC, end up with aberrant connectivity (result obtained from studies on mice) [19]. Defective neurodevelopment is the result of the expression of the *DISC1* gene mutation (which we presented in the previous subchapter). These abnormalities in the interconnection of neural networks have been associated with behavioral changes marked by a significant reduction in social activity. Also, at the level of the PFC, in addition to affecting the well-known dopaminergic pathways, the possibility of altering the kynurenine pathways, whose extremely important role is given by the generation of cellular energy, was also investigated. Kynurenine is also considered the bridge between the neuroendocrine system and the immune system [159]. Its alterations were not only recorded in the PFC, but also in the cerebellum, where there is a general dysfunction of the cerebello-thalamo-cortical circuit (associated with the negative symptomatology of schizophrenia). The dysfunction could affect the serotonin degradation metabolite [160].

Because a reaction does not come by itself, glutamate is also affected, at the level of the medial PFC, by kynurenine dysfunction [161].

Motor cortex

The motor cortex is another extremely important region affected by psychosis. Whether the deficits stem from dysfunction in this region or are more the result of aberrant modulation has yet to be determined [162]. In this area there are certain connectivity difficulties, which affect motor function. This aspect has a negative impact on the

social life and QoL of the patients. A small proportion of those diagnosed with schizophrenia develops catatonic symptoms, which consist of severe loss of motor functions. Studies [163] have shown that in these severe cases there is a significant alteration of the connections between certain specific areas: the splenium of the *corpus callosum*, the right peduncle of the cerebellum and the right internal capsule.

The auditory cortex

It is one of the brain regions associated with positive symptoms, specifically auditory hallucinations (the most common symptom). This type of hallucination has been attributed to significant structural changes in the superior temporal gyrus and temporal planum [164]. The changes resulted in cortical asymmetry, which prevents interconnection in certain portions [165]. Also, at the cortical level, gray matter has a reduced volume (a possible cause could be reduced synaptic connectivity), which has been associated with altered auditory activity [166]. Neuroimaging measurements showed that patients who developed auditory hallucinations had a smaller auditory cortex, but the area of Heschl's gyrus (the primary auditory cortex) was similar to that of healthy subjects.

Cerebellum

Another major area affected in schizophrenia is the cerebellum [167]. Among other functions, this region is also involved in attention, working memory, verbal learning, sensory discrimination, control of motor activity, in motor learning and has a sensorimotor calibration, depending on the context in which the individual is. Any structural change leads to deficits of the mentioned functions. Variations in the *NRG1* gene appear to play a role in alterations in glutamate levels in the prefrontal-thalamo-cerebellar that cause functional deficits in schizophrenia [168]. Poor connectivity between the prefrontal area and the cerebellar area has been associated with severe negative symptoms [169].

Visual impairment in schizophrenia

A remarkably interesting finding is the visual impairment associated with schizophrenia [170]. So, it is demonstrated (again) that the disorder is one of, if not the most complex psychiatric disorder. In addition to deficits (in the brain) caused by neurodevelopment there are also neurodegenerative deficits, even at the level of the corneal nerve, which is thinned [171]. A decrease in volume has also been observed, which implies microvascular changes in the retina, directly proportional influenced by the evolution of the disorder [170, 172, 173]. These pathologies are specific to the elderly, but psychosis triggers them from the onset, or even earlier. There is fairly clear evidence of visual processing deficits in individuals even before the onset of the disorder [174].

Although people affected by schizophrenia have an apparently regular course until the onset of symptoms from the point of view of cognitive and social functioning, brain development is not carried out in the same way. The genetic studies we have discussed indicate that polymorphisms or mutations, at the gene level, prevent neuronal migration and development [175] in the cerebral cortex. This aspect places psychosis among neurodevelopmental disorders. Although it has been assigned to this category, there are still many question marks about the neural trajectory, during the structural development of the brain, in schizophrenia. We know that the interconnection of regions occurs poorly, but there are still many gaps in the information we have. So, we cannot say very clearly what are the exact mechanisms that determine these functional alterations.

Conclusions

Dopaminergic receptors regulate neurosynaptic transmission, important being DAT and VMAT2. The function of DA D2 receptors was best known because the first discovered neuroleptics acted at this level. Presynaptic D2 autoreceptors are located at the level of the axon terminal and in the somatodendritic area. Among the cortical structures involved, we note the *substantia nigra* and the striatal nucleus (the nigrostriatal dopaminergic pathway), the tegmentum area and the *nucleus accumbens*, the thalamus, the hypothalamus, the pituitary gland, the dorsolateral PFC along with the ventromedial PFC. The mesolimbic dopaminergic pathway is responsible for positive symptoms. It intervenes in the regulation of emotions and behaviors. The hyperactivation of this pathway is responsible for hallucinations and delusional ideas. The dorsolateral PFC is involved in negative symptoms as well as in positive ones, these being dictated by a hypoactivity at this level. The article also focused on the consequences of the neurodevelopmental abnormality regarding the glutamatergic system (NMDA). Among the susceptible genes in schizophrenia, we highlighted *DISC1*, *COMT*, *MAO-A/B*, *GAD67* and *NRG1*, and dysbindin-1 protein, on which many modern psychotropic drugs are focused.

Conflict of interests

The authors declare that they have no conflict of interests.

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