REVIEW

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Biomarkers in schizophrenia – past, present and future

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Abstract

Schizophrenia is a complex and debilitating neuropsychiatric syndrome. Although research into the etiology of this pathology has advanced considerably, consistent results are still awaited. The discovery of biomarkers that could underlie diagnosis and treatment could revolutionize the management of this pathology, and approaching biomarkers from an evolutionary perspective, along with the multitude of existing and future studies, can provide important information. The complexity of this multifactorial pathology requires its approach from an integrated and multidisciplinary perspective, which considers research on neurodevelopment, genetics, imaging and, last but not least, neurobiological research. The present material aims to bring to light a series of recent research, as well as the approach to this pathology from an evolutionary perspective of neurodevelopment, in the hope that it will constitute an attractive point of view that could imagine new ways of approaching this pathology.

Keywords: schizophrenia, biomarkers, evolutionism, neurodevelopment.

Introduction

Schizophrenia, known as a severe and debilitating illness, presents a wide range of symptoms including delusions, hallucinations, disorganized behavior, affective and cognitive disorders, social dysfunction, and other types of symptoms that may vary from one case to another depending on a series of intrinsic and/or extrinsic factors [1, 2]. Approximately 1% of the global population is affected by this illness [3]. Mental and behavioral features in schizophrenia can be classified into three categories. The first category brings together negative symptoms, which include poverty of speech and spontaneous movements and blunting of affect [4]. Decreased emotional expressiveness and avolition are two negative symptoms frequently encountered in schizophrenia [5]. The second category includes the disorganization syndrome, which refers to thought disorders; this category includes: fragmentation of ideas, weakening of associations, and discordant and tangential emotional expressiveness. The third category is represented by the distortion of reality, symptoms such as hallucinations and delusions being grouped together under the name of positive symptoms [4].

Cognitive deficits are considered key factors in schizophrenia, and their optimal assessment can beneficially influence both the treatment and management of patients with this pathology [6]. Stagnation or evolution of cognitive deterioration during the course of the disease are two controversial topics. Some studies suggest that cognitive deficits stagnate as the disease progresses, while other studies indicate a progression of cognitive deterioration, including during periods of remission of the disease [7]. Cognitive deficits can manifest even before the onset of the disease and can be maintained for several decades [8, 9]. The functioning of schizophrenic patients still raises issues regarding unitary and homogeneous acceptance that would satisfy optimal criteria for standardizing this pathology [10].

Although the etiology of schizophrenia is still unknown, the hypothesis regarding the significant involvement of genetic mechanisms is supported by research that attempts to establish the existence of a possible correlation between genetic variation and normal cellular activity [11, 12].

In recent decades, the scientific approach to schizophrenia has focused on the study of biomarkers, measurable biological characteristics that could provide valuable information on the pathophysiology of schizophrenia, starting from diagnosis and response to treatment, to the evolution and prognosis of the disease. The multitude and diversity of information obtained from research makes it quite difficult to have a unified and structured approach to biomarkers. However, there are studies that have highlighted possible associations between peripheral, electrophysiological, neuro-imaging biomarkers in schizophrenia [13], considering the particularities of some blood biomarkers, inflammatory biomarkers, intestinal microbiota, proteomics, as well as other biological components. The identification of biomarkers for schizophrenia would have multiple benefits both in the diagnosis and prognosis of the disease and in the optimal adaptation of treatment [14, 15].

Poor response to pharmacological treatment has important social and economic implications. Examining genes that confer increased risk in schizophrenia spectrum disorders could help to more clearly differentiate between patients with good and poor response to treatment [16].

Studying biomarkers from an evolutionary perspective

Some brain structures in the newborn brain are only partially formed, while others will form in the following years, processes that take place simultaneously in different regions of the brain, not sequentially. At the level of each brain formation that is present at birth, there are a series of genes that may be involved in the development of pathologies in the psychiatric sphere and beyond [4], from which can be enumerated:

HOX genes

The *HOX* genes, engrailed 1 (*EN1*) and engrailed 2 (*EN2*), play a very important role in the development and early organization of the nervous system, participating in the formation of brain areas [17, 18] and the Wnt signaling pathway networks are involved in cell signaling and neuronal migration and differentiation [19]. Some studies have shown the involvement of *HOX* genes in schizophrenia but also in other pathologies, such as epilepsy, mental retardation and autism spectrum disorders [20], as well as the *EN1* gene that has been associated with schizophrenia symptomatology [21]. The engrailed homeoprotein (En1/En2, collectively En1/2) represents an important survival factor of neurons in early development but also has neuronal protective functions in adulthood [22].

BDNF

Brain-derived neurotrophic factor (BDNF) is a protein with a major role in the development and function of the nervous system, having implications in the survival, growth and development of neurons as well as in the formation of synapses and in the development of brain structures such as the cortex, hippocampus, and cerebellum, being involved in synaptic plasticity processes and in cognitive processes such as memory and learning [23]. BDNF deficiency has been associated with a number of disorders, such as depression, schizophrenia, and Alzheimer's disease, but also with problems with memory and cognitive performance. BDNF is considered a possible biomarker of schizophrenia, due to its important role in neurogenesis and neuroplasticity, as well as its impact on cognitive functions such as memory and learning. Decreased BDNF levels have been associated with cerebral atrophy and neurodegenerative diseases. Variation in BDNF levels is found in both schizophrenia and other psychiatric pathologies, such as bipolar disorder, which draws our attention to its impact in this field. However, since results observed in several studies are contradictory regarding the positive or negative correlation of BDNF with schizophrenia and other psychiatric disorders, caution is required in attributing the role of biomarker to this factor [24].

Neurotrophin-3

Changes in neurotrophin-3 (NT-3) expression in schizophrenia patients, recommend it as a potential biomarker for this pathology. NT-3 has important roles in early neurodevelopment, in the processes of embryogenesis and organogenesis and in the processes of neuroplasticity [25].

Wnt signaling pathway

A study that followed the expression of Wnt signaling pathway genes did not find significant changes in schizophrenia patients [26], while another study observed that dysregulation of the Wnt signaling pathway is associated with neuroinflammation in schizophrenia [27, 28].

FOXP2 gene

Forkhead box P2 (*FOXP2*) is a gene involved in language development and is essential in forming connections between the temporal and motor cortex, facilitating language development. Some studies have shown that the *FOXP2* gene, which is involved in language and speech development [18, 29] has not been associated with schizophrenia [30, 31], but only with immediate memory in schizophrenic patients [31].

CNTNAP2 gene

Contactin-associated protein-like 2 (*CNTNAP2*) gene also contributes to the development of language and cognitive processes. The *CNTNAP2* gene has been identified in a variety of pathologies, such as schizophrenia, obsessive–compulsive disorder, intellectual disability, autism, Hopkins syndrome, etc. It is believed that deletions of *CNTNAP2* alleles lead to a series of abnormalities at the protein level [32]. The *CNTNAP2* gene encodes a protein with a role in the development and connection of presynaptic and post-synaptic neurons, being also involved in mediating signal transmission across synapses [33], which is a possible explanation for neuronal hypoconnectivity in autism and other neurodevelopmental disorders [32].

FMRP

Fragile X mental retardation protein (FMRP), a ribonucleic acid (RNA) binding protein, has an important expression in neurons because it mediates neurotransmitter release, synaptic transmission and neuroplasticity [34, 35]. Significant reductions in FMRP have been identified in subjects with schizophrenia, bipolar disorder and major depression, in the lateral cerebellum, but no changes in FMRP messenger RNA (mRNA) have been reported in these pathologies [36, 37].

MEF2

Myocyte enhancer factor 2 (MEF2) proteins are considered critical factors in the neurodevelopmental process because they regulate the gene expression of a large number of genes and have a very important role in the first years of life in cellular differentiation, synaptic remodeling, the correct connection of different brain areas and neuronal survival, mutations occurring at this level being linked to the risk of neurodevelopmental disorders and mental illnesses [38–40].

NRXN1 gene

Neurexin 1 (*NRXN1*) gene plays an important role in synapse formation and neuronal communication, being essential in the development of the central nervous system (CNS) and in the regulation of some cognitive functions [41]. A number of studies have shown the involvement of *NRXN1* in a number of disorders from the schizophrenia and autism spectrum [42, 43], intellectual disabilities, mood disorders, congenital malformations and others [42].

Genetic biomarkers

The last decades have marked the discovery and deeper understanding of some genes involved in schizophrenia, bringing to light neurobiological mechanisms that could be involved in this pathology and recommending them as potential biomarkers [44, 45].

Interneuronal connections at the brain level, which underlie mental processes, influence human behavior. Genes have an important role in shaping behavior based on the influence they have, through their component proteins, on the distribution and consistency of interneuronal connections. The modification of protein synthesis is what determines neuronal functioning, thus producing a series of events in which genes are indirectly involved. Gene activation and inactivation, processes that underlie epigenetic mechanisms, arise by modifying the structure of chromatin [the substance made up of histones, proteins around which deoxyribonucleic acid (DNA) is packaged] that determine the characteristics of a cell. The modification of proteins that are part of chromatin is influenced by a series of extrinsic factors, such as the environment and the medication administered, as well as intrinsic factors, among which we can mention the processes controlled and regulated by neurotransmitters, the methylation process, the phosphorylation process and other processes that take place at this level [46].

The hypothesis that cell differentiation represents a genetic pattern that remains stable throughout life has been refuted by studies in which it was observed that some mature neurons change their characteristics by producing *de novo* alterations of the epigenome, by modifying the equilibrium state of some epigenetic patterns. These alterations can be consequences of childhood abuse, conditioned fear, anxiety states, stress in adulthood, nutritional deficiency, abuse of psychoactive substances and others. Equally, a series of new experiences, including psychotropic medication, psychotherapy, the learning process through which spatial memory is formed and others, can influence neurons in a positive sense and thus a series of genes can be activated. In other words, inactive genes can become active, and active ones can become inactive [46, 47]. Epigenomic regulatory mechanisms can vary in magnitude and in the persistence of the effects over time [48].

Research that recommends a series of genes as potential biomarkers for schizophrenia has been based, among other things, on the methylation processes of histones, since it has been found that the methylation process of these proteins can inactivate genes, resulting in the cessation of RNA production, while demethylation can activate them. Depending on the agent that determines methylation (medication, environment, optimal or not the development of the neurotransmission process) certain genes will be expressed or will remain epigenetically inactive [46]. Along with methylation processes, gene activity is also regulated by the processes of DNA hydroxymethylation, modification of some proteins (histones), processing of RNA and RNAs that do not code for proteins, and chromatin remodeling. RNAs that do not code for proteins have a very important role because they are involved in developmental processes, but also in neuroplasticity. The patterns on which methylation reactions occur are unique throughout life. Both at the level of chromatin and DNA methylation, a series of changes occur that may be involved in mental and neurological disorders, but also in the aging process [49, 50].

Neuroepigenetic mechanisms are involved in the dynamic plasticity of the brain, which results in changes in brain architecture during development [48, 50]. In people with schizophrenia, important changes in RNA profiles have been observed that cause dysregulation of gene expression, with microRNA (a type of non-coding RNA) being associated with synaptic function, neurodevelopment and neuroinflammation [51]. Circular RNA also plays an important role in normal developmental processes, with some studies highlighting its involvement in a number of neuropsychiatric diseases, including schizophrenia [52].

The identification of molecular biomarkers that reach the blood remains a challenge due to their minimal amount present in the blood and their high degree of fragmentation. Peripheral blood mononuclear cells are currently considered a rich source of biomarkers, a claim based on the modification of the RNA signature and the methylation profile. The recording of changes in the methylation process and the RNA signature is a testimony to the source of biomarkers represented by peripheral blood mononuclear cells. However, the presence of biomarkers that reach the blood faces a series of difficulties due to their high degree of fragmentation and their tiny amount [50, 53, 54].

Genes that show an increased level of expression have a considerable impact on cellular and metabolic processes, and monoamine disruption may play a role in the development of schizophrenia. The explanation is due to the fact that monoamine transporters [encoded by the solute carrier family 18 member A1 (*SLC18A1*) gene] are involved in the storage of neurotransmitters, located in the terminals of presynaptic neurons, such as dopamine, serotonin, adrenaline and noradrenaline. In schizophrenic patients, it has been determined that the *SLC18A1* gene shows increased levels of expression [55].

To identify possible molecular pathways associated with the risk of psychosis, gene and genetic variant analysis was used, while gene transcription analysis revealed a series of disorders at this level. In a study in which six gene modules were discovered, they were divided into two clusters. The first cluster had positive correlations, and the component genes were associated with neurotransmitter metabolism. The second cluster had negative correlations and the genes in its component were correlated with inflammatory pathways. Among the potential genes in the first cluster that could be involved in schizophrenia, we find sirtuin 1 (*SIRT1*), serine/threonine kinases, ubiquitin-like modifier activating enzyme 3 (*UBA3*), neuroblastoma RAS proto-oncogene guanosine triphosphatase (GTPase) (*NRAS*), TIA1 cytotoxic granule-associated ribonucleic acid (RNA) binding protein (*TIA1*), splicing factor 3b subunit 1 (*SF3B1*) and ubiquitin-conjugating enzyme E2 N (*UBE2N*) (Table 1) [56].

The presence of genes in the second cluster supports the immunological and inflammatory hypothesis of schizophrenia and therefore the possible role of inflammatory markers in the severity of symptoms in this pathology. The Toll-like receptor signaling pathway and the neurotrophin pathway, between which complex interactions are assumed based on cellular communication between astrocytes and microglia, have an important role in neuronal maturation, differentiation and survival as well as in synaptogenesis and neuroplasticity

of the adult brain. Furin, an important gene included in the second cluster, has also been studied through the lens of von Willebrand factor (vWF), which represents a substrate of furin and is known as a marker of inflammation, endothelial cell activation and is associated with brain morphology and psychotic symptoms. Other genes involved in the second cluster were mitogen-activated protein (MAP) kinase kinase 7 (*MAP2K7*), a gene correlated with functional brain plasticity but also with cognitive processes, and forkhead box O3 (*FOXO3*), a transcription factor that has multiple functions in both neuronal development and the adult brain and is implicated in schizophrenic pathology [56].

Table 1 – *Clusters associated with neurotransmitter metabolism and metabolic and inflammatory pathways*

Cluster associated with neurotransmitter metabolism	Cluster associated with metabolic and inflammatory pathways
SIRT1	*Furin – vWF*
Serine/threonine kinases	*MAP2K7*
UBA3	*FOXO3*
NRAS	
TIA1	
SF3B1	
UBE2N	

FOXO3: Forkhead box O3; *MAP2K7*: Mitogen-activated protein (MAP) kinase kinase 7; *NRAS*: Neuroblastoma RAS proto-oncogene, guanosine triphosphatase (GTPase); *SF3B1*: Splicing factor 3b subunit 1; *SIRT1*: Sirtuin 1; *TIA1*: TIA1 cytotoxic granule-associated ribonucleic acid (RNA) binding protein; *UBA3*: Ubiquitin-like modifier activating enzyme 3; *UBE2N*: Ubiquitin-conjugating enzyme E2 N; *vWF*: von Willebrand factor.

A series of bioinformatic methods have been developed that seek to detect genetic signatures that may be immunologically associated with schizophrenia. Another study that had this goal detected a series of genes that could be involved in the onset and evolution of schizophrenia. These genes were divided into two clusters, depending on the increased or decreased immunological values. The level of gene expression in the two categories was associated with the response to interferon-beta (IFN-β) and interferon-gamma (IFN-γ), as well as immunoglobulin G (IgG) binding. Eight genes (Table 2) were highlighted that are involved in immunological processes in schizophrenia, namely: *IFITM1*, *IFITM3*, *GBP1*, *GBP2*, *BST2*, *CD44*, *FCER1G*, *HLA-DRA*, *FCGR2A*, *FCGR3B* and *IFI16* [57].

Table 2 – *Genes associated with immunological processes in schizophrenia*

Gene	Official full name
IFITM1	Interferon (IFN)-induced transmembrane protein 1
IFITM3	IFN-induced transmembrane protein 3
GBP1	Guanylate-binding protein 1
GBP2	Guanylate-binding protein 2
BST2	Bone marrow stromal cell antigen 2
CD44	Cluster of differentiation 44 (CD44) molecule
FCER1G	Fc fragment of immunoglobulin E (IgE) receptor Ig
HLA-DRA	Major histocompatibility complex, Class II, DR alpha
FCGR2A	Fc gamma receptor IIa
FCGR3B	Fc gamma receptor IIIb
IFI16	IFN-gamma inducible protein 16

Currently, the role of the complement C3 (*C3*), transforming growth factor beta 1 (*TGFB1*), *PIK3CD*, *PDE4B*, *FAM69A*, *IFITM1* and protein phosphatase 3 catalytic subunit gamma (*PPP3CC*) genes in neuronal function is known, the relevant *C3*, *TGFB1*, *PIK3CD*, *PDE4B*, *FAM69A*, *IFITM1* and *PPP3CC* genes in immune dysfunction and neuroinflammation in schizophrenia, as well as the *PIK3CD*, *PDE4B*, SH3 and multiple ankyrin repeat domains 2 (*SHANK2*) and NudE neurodevelopment protein 1 (*NDE1*) genes involved in neuronal development and also significant in schizophrenia pathology. In the pathogenesis of schizophrenia, the role of the complement receptor 1 (*CR1*), complement receptor 2 (*CR2*), cluster of differentiation 55 (*CD55*) and *C3* genes, components of the complement system, as well as the role of the neuronal development genes, *PIK3CD* and *PDE4B*, is emphasized. The involvement of these genes in the pathology of schizophrenia emphasizes the importance of investigating the mechanisms of the immune system (Table 3) [58].

Table 3 – *Genes associates with the pathogenesis of schizophrenia*

Component genes of the complement system	Genes involved in neurodevelopment
CR1: Complement receptor 1; complement C3b/C4b receptor 1	*PIK3CD*: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
CR2: Complement receptor 2; complement C3d receptor 2	*PDE4B*: Phosphodiesterase 4B
CD55: Cluster of differentiation 55 (CD55) molecule	
C3: Complement C3	

A study that highlighted two molecular subtypes recommends these genes as potential biomarkers of schizophrenia. From the total number of genes, genes related to ribosomes, the ubiquitin-proteasome system (UPS), mitochondria and mRNA processing were selected for study. It was found that defective transcription of ribosomal RNA associated, among others, with schizophrenia, is found both in lymphocytes and in the brain. It is believed that the increased expression of ribosomal genes is determined by oxidative stress, as their attempt to combat it. Another hypothesis suggests that the accumulation of defective proteins in neurons could be due to the dysfunction of some ribosomes, which could contribute to the onset of schizophrenia. Defective variations that can occur within UPS have been associated with schizophrenia. Thus, both ribosomal genes and the UPS may represent factors involved in the development of schizophrenic pathology [59].

Some studies have highlighted the alteration of mitochondrial dynamics in patients with schizophrenia. The regulatory activity of circular RNAs, as well as the fact that they influence mitochondrial functions, are aspects that must be considered due to their involvement in schizophrenia and a number of neurological disorders. Investigation of the relationship between mitochondrial dynamics and syncytin-1 (endogenous retrovirus group W member 1 – *ERVWE1*), a protein found in human DNA, has revealed that mitochondria, as well as their functional dynamics, can be disrupted by endogenous human retroviruses, considered by some authors to be a key factor in schizophrenia [60].

Another study on epigenetic biomarkers in schizophrenia identified three genes (insulin-like growth factor-2 mRNA-binding protein 1 – *IGF2BP1*, centromere protein I – *CENPI*, and proteasome activator subunit 4 – *PSME4*) that showed distinct methylation patterns in schizophrenic patients. These genes were shown to have a functional link to schizophrenia [61].

Brain biomarkers

The identification of potential brain biomarkers, in addition to genetic biomarkers, may contribute to establishing an objective diagnosis of schizophrenia and may provide important data in the study of this pathology [62]. It has been found that in schizophrenic patients there are a series of impairments that occur during neurodevelopment but also in the processes of neurogenesis and neurotransmission [63–65]. It is known and accepted that neuroblastic differentiation, migration, neuronal multiplication and neuronal connectivity, in the case of adults, represent processes determined by the human genome [4]. Inheritance of sets of genes that carry a degree of risk confers only a predisposition to a mental illness, the molecular abnormalities encoded in genes may remain silent in the absence of a stress factor; otherwise, the respective genes become active, thus determining the appearance of the mental disorder [46]. The process of neurogenesis, which is limited to certain brain regions, is dynamic and influenced by a multitude of factors, both intrinsic and extrinsic [49], and is achieved through the generation of neuroblasts. Defective proliferation and differentiation of neuroblasts is linked, among other pathologies in the psychiatric sphere, to schizophrenia, contributing to cognitive decline [66]. The expressions of genes considered to be involved in schizophrenia differ if we relate them to cell types and brain regions [11]. It has been emphasized that genes associated with schizophrenia present numerous pyramidal neurons and spiny neurons [67].

Astrocytes are thought to contribute significantly to the etiology and pathogenesis of schizophrenia, playing an important role in neuroprotection, neurodevelopment, neuroplasticity, and immune functions [68]. Astrocytes, oligodendrocytes, and microglia, which are molecularly and functionally distinct components of the CNS, represent between 20% and 40% of the cell types in the brain [69]. Cognitive and olfactory symptoms in schizophrenia, glutamatergic signaling, synaptic plasticity, and demyelination have been associated with astrocyte dysfunction [70]. The discovery of 25 distinct brain cell types that harbor genes whose function is disrupted in both astrocytes and subpopulations of excitatory neurons supports the importance of astrocytes in schizophrenic pathology [71]. However, postmortem data does not suggest notable changes in the density or number of astrocytes in the cortex in schizophrenia. A meta-analysis investigating microglia density in postmortem tissue observed a significant increase in microglia density and proinflammatory genes associated with microglia in schizophrenia. Microglia play an important role in pathological processes, one of their roles being to search for brain lesions, but they also have important roles in normal processes, modifying synaptic architecture depending on the subject's experiences [72].

The basic function of chemical neurotransmission is the exchange of information between the DNA of the presynaptic genome and the DNA of the postsynaptic genome, where the postsynaptic reaction can last for days, weeks, or even a lifetime. The components involved in this process can be influenced and modified by a number of internal and external factors, including psychotropic medication [46]. Studies have shown possible links between the pathophysiology of schizophrenia and oxidative stress, one argument being high oxygen consumption at the cerebral level [73–75].

Equally, the impact that antipsychotic treatments can have on the oscillation of oxidative stress levels has been highlighted, with typical and atypical antipsychotics having different antioxidant capacities. The effect of medication on oxidative stress should also be mentioned, considering the different subtypes of pathologies in the field of schizophrenia [76].

It has also been suggested that drugs targeting transcription factors have an increased potential in schizophrenia. The imbalance of the redox system, which could be based on genetic mechanisms, may be involved in the etiology of schizophrenia. Environmental factors are also important variables that affect the normal functioning of genetic mechanisms and expression and thus contribute to the alteration of redox signaling, producing mitochondrial dysfunction and metabolic abnormalities, processes that disrupt neuronal development [77].

A mechanism that is believed to play an important role in the triggering of schizophrenia is the immune system response, the dysregulation of this system being of a very complex nature. The possible involvement of energy metabolism in the etiology of schizophrenia could explain the complex structural, functional and metabolic changes that occur in the brain. The increase in immune markers in acute psychotic states supports the hypothesis of immune dysregulation. Increased levels of inflammatory factors such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-17 and C-reactive protein (CRP) are significantly associated with certain psychiatric disorders, such as schizophrenia. Mitochondrial dysfunction and imbalance of the redox system, as effects of energy metabolism dysregulation, alter creatine kinase activity in the prefrontal cortex. Negative symptoms in schizophrenia have been confirmed by neuroimaging by changes in the prefrontal cortex and cingulate gyrus. Decreased levels of dopamine, serotonin and glutamate may also play an important role in the onset of schizophrenia. Physiological aging as well as brain pathology are processes that are constantly influenced by both genetic and environmental factors. The overlap between metabolic processes, which occur early in brain formation, and gene action in pathologies such as schizophrenia or depression, have an important impact on brain architecture but also on the connectivity between different regions leading to structural abnormalities, such as reduced CNS volume, reduced functional dynamics in the medial prefrontal cortex and increased microglial activity in schizophrenia [78, 79], as well as disruptions in white matter integrity and reductions in gray matter volume [80].

The inflammatory process is considered to be a potential factor in the evolution of schizophrenia, but also of major depressive disorder, the changes in some inflammatory cytokines attesting to this hypothesis. Emotional and cognitive functions, sensitive to inflammation, are affected by short-chain fatty acids, it being proven that they influence the gut–brain axis, and the changes in their values have been associated with both schizophrenia and major depressive disorder. The cytokines involved in this process are CRP, IL-6 and TNF-α. Increased values of IL-9, IL-4 and transforming growth factor-beta 1 (TGF-β1) have been found in schizophrenic patients. At the same time, the severity of symptoms has been associated with increased values of 4-methylvaleric acid [81].

Another study that highlighted the inflammatory process as a potential endophenotype of schizophrenia brought to the fore a series of hypotheses, for argumentative purposes, namely: increased levels of cytokines involved in neuro-inflammation, such as IL-10, S100B protein (with activities similar to neuroinflammatory cytokines) [82]. The systemic inflammation observed in schizophrenia is also a hallmark of aging [83].

It is important to emphasize that contracting an infection causes the body to reallocate energy to the immune system, the affected individual becoming apathetic, socially withdrawn and motivation and ability to concentrate diminish. The relevance for the immune system is the early period of development; the microbiome, among other elements of the immune system, helps to configure the brain in the first years of life [84].

Some research supports the idea that examining metabolic changes in the blood and brain may provide deeper diagnostic information and may be helpful in the management of schizophrenia. The significant correlations with clinical tests and brain imaging of metabolites, such as cortisol, glutamate and lactate, underline the importance of metabolomics as a potential provider of biomarkers for schizophrenia, an objective aligned with the *World Health Organization* (WHO) requirements regarding the need to discover such biomarkers. Decreased immunological markers have been associated with increased levels of lactate and cortisol. Altered lactate in schizophrenic patients suggests changes in energy metabolism, both in aerobic and anaerobic processes. Cortisol dysregulation, as a possible response to stress but also as a consequence of the administration of antipsychotic treatments, is frequently encountered in schizophrenia. More severe forms of schizophrenia are linked to glutamatergic dysfunction, as evidenced by low levels of this neurotransmitter. The correlation between glutamate and hostility highlights its role in the emotional and behavioral dysfunctions encountered in schizophrenia [85].

A study that proposed a "feature selection" method based on preserving local structure and eliminating redundancy, from imaging data, found that the functional connectivity of the subthalamus–cerebellum networks and the thalamus–caudate networks are weakened in schizophrenia patients, suggesting that abnormalities in the connection of the thalamus with other brain structures may contribute to the appearance of negative symptoms. The connectivity characteristics of functional networks could represent potential biomarkers in schizophrenia [86].

Measurement of dopamine synthesis and assessment of postsynaptic and presynaptic dopamine receptor occupancy, using radionuclide imaging, may contribute to the accuracy of diagnosis and treatment in schizophrenia spectrum disorders [87].

Imaging studies have revealed some links between the architecture of brain networks and cortical changes in schizophrenia. The denser the interconnected regions, the more prone they are to morphological changes. Depending on the different stages of the disease and the individual symptoms, intense connectivity has been observed in temporal, paralimbic and frontal regions. However, a causality between the changes in brain morphology and the configuration of the underlying networks has not been demonstrated [88]. Neuroimaging has also revealed disturbances in the integrity of white matter, as well as reductions in the volume of gray matter. In a large study that aimed to identify changes in local functional connectivity using the regional homogeneity (ReHo) technique, it was found that in the bilateral medial superior frontal gyrus ReHo was significantly higher in schizophrenic patients, and in the bilateral postcentral gyrus, right precentral gyrus and right middle occipital gyrus ReHo was lower. These results support changes in functional connectivity in schizophrenia pathology [89].

It is believed that the disorders that occurred in the transmission mechanism of dopamine and glutamate are related to dysfunctions that occur at the level of the thalamus and its connections with other cortical formations. The thalamus has a central role in the presence of schizophrenic symptoms due to its involvement in executive functions, cognitive processes, integration and processing of sensory information [90]. In a study that targeted individuals with early onset of schizophrenia, thalamocortical disconnections were found involving the prefrontal, auditory, visual cortex, cerebellum, somatomotor network and limbic network [91, 92].

Similarly, it has been shown that there is a disruption of neuronal activity even when schizophrenic patients perform a series of activities spontaneously [93].

The thalamus is considered a relay point because it is involved in numerous information exchanges within the thalamo-cortico-cerebellar network [94]. Thalamocortical connectivity has been proposed as a potential biomarker for schizophrenia [91, 93].

However, there are also studies that refute the theory according to which in schizophrenia there would be a certain disconnection in certain brain regions, more precisely in the cingulate cortex which has been investigated in detail by delimiting six regions – the subgenual anterior cingulate cortex (sACC), the pregenual anterior cingulate cortex (pACC), the middle anterior cingulate cortex (aMCC), the posterior middle cingulate cortex (pMCC), the posterior cingulate cortex (PCC) and the retrosplenial cortex (RSC) – because in the resting state of the brain no disconnections of these regions were observed in schizophrenic patients [95].

It is important to note that the inconsistent results may be due to the fact that the research is limited to the study of isolated brain regions and not the entire brain [94].

Multisensory integration deficits have been found in the temporal cortex, frontal and parieto-occipital regions, which can be attributed to reduced or aberrant neural activity, in schizophrenic patients. However, the differences and deficits observed in neural activity were not based exclusively on deficits found in performance [96].

While some studies have reported reduced activity in the ventral striatal area, in which reward anticipation is integrated, and which has been associated with negative symptoms in schizophrenia [97, 98], other studies have not reported an association of the ventral striatum with negative symptomatology, but rather with the symptom of apathy, which may indicate a link between apathy and the reward system. Activity in this brain area has also been proposed as a biomarker for schizophrenia [99].

The observed abnormalities in the functional and

structural connectivity of the corticostriatal system suggest that measuring the function of this circuit may be a potential biomarker for schizophrenia [100].

Conclusions

Approaching biomarkers for schizophrenia from multiple perspectives, genetic, neurobiological, neurodevelopmental, considering the multifaceted aspects of the disease, could make significant contributions to the understanding of this pathology, providing more refined information that would serve both diagnosis and individualized treatments, thus leading to a significant improvement in the lives of these patients.

Conflict of interests

The authors declare that they have no conflict of interests.

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