Progress in Neuropsychopharmacology & Biological Psychiatry 120 (2023) 110626

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Biological hypotheses, risk factors, and biomarkers of schizophrenia

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ARTICLE INFO

Keywords:
Biological hypothesis
Biomarker
Neurochemistry
Neuroplasticity
Risk factor
Schizophrenia

ABSTRACT

Both the discovery of biomarkers of schizophrenia and the verification of biological hypotheses of schizophrenia are an essential part of the process of understanding the etiology of this mental disorder. Schizophrenia has long been considered a neurodevelopmental disease whose symptoms are caused by impaired synaptic signal transduction and brain neuroplasticity. Both the onset and chronic course of schizophrenia are associated with risk factors-induced disruption of brain function and the establishment of a new homeostatic setpoint characterized by biomarkers. Different risk factors and biomarkers can converge to the same symptoms of schizophrenia, suggesting that the primary cause of the disease can be highly individual. Schizophrenia-related biomarkers include measurable biochemical changes induced by stress (elevated allostatic load), mitochondrial dysfunction, neuroinflammation, oxidative and nitrosative stress, and circadian rhythm disturbances. Here is a summary of selected valid biological hypotheses of schizophrenia formulated based on risk factors and biomarkers, neurodevelopment, neuroplasticity, brain chemistry, and antipsychotic medication. The integrative neurodevelopmental-vulnerability-neurochemical model is based on current knowledge of the neurobiology of the onset and progression of the disease and the effects of antipsychotics and psychotomimetics and reflects the complex and multifactorial nature of schizophrenia.

1. Introduction

Schizophrenia is a mental disorder (heterogeneous syndrome) that can manifest with (i) delusions, hallucinations, extremely disordered thinking (speech), disorganized behavior (collectively positive symptoms), (ii) flat affect, amotivation, anergy, and failure to maintain hygiene (negative symptoms) (Biedermann and Fleischhacker, 2016), along with many more symptom domains (behavioral, cognitive, physical, and psychosocial). Impairment in cognition is one of the key features underlying disabilities in schizophrenia (Seidman and Mirsky, 2017). The median lifetime morbid risk for schizophrenia is approximately 0.72% (McGrath et al., 2008), and the onset of symptoms of the disease usually occurs between late adolescence and the early 30s of life. Its etiology remains insufficiently known; evidence supports a multifactorial neurodevelopmental pathogenesis for schizophrenia (Fallon et al., 2003). The pathophysiology of the onset and progression of schizophrenia and sensitive and specific biomarkers have not yet been reliably identified.

In terms of neurochemistry and neurobiology, schizophrenia is a consequence of impaired development of neural circuits and impaired signal transduction through chemical synapses due to abnormal activity of neurotransmitter receptor systems and downstream signaling pathways. Key concepts in the biological hypotheses of schizophrenia are (i) risk factors and biomarkers, (ii) neurodevelopment, (iii) synaptic and nonsynaptic neuroplasticity, (iv) brain neurochemistry, and (v) antipsychotic medication (Fig. 1).

Risk factors are associated with a disease because they are in the causal pathway leading to the disease. Risk markers are associated with the disease but need not be causally linked; they may be a measure of the disease process itself. Risk factors and markers associated with schizophrenia may be categorized into genetic and epigenetic, environmental, neurodevelopmental, and regulators of brain plasticity and chemistry.

Biomarkers (biological markers) are measurable quantities (genetic and epigenetic, proteomic, metabolomic, histopathologic, neuroimaging, neurophysiological, and neurochemical) that are indicators of specific normal and pathological processes in cells, tissues, or organisms at a given time, and that can be used to diagnose and monitor disease, including biochemical and physiological responses to pharmacological and other therapeutic interventions. Biomarkers of schizophrenia include objectively measurable risk factors (e.g., genetic and epigenetic)

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https://doi.org/10.1016/j.pnpbp.2022.110626
Received 29 April 2022; Received in revised form 24 August 2022; Accepted 25 August 2022
Available online 31 August 2022

and indicators of neurodevelopment, neuroplasticity, and neurochemistry.

Neurodevelopment of neural circuits from the first synapses to cognitive and behavioral regulation includes the following major events (Reichard and Zimmer-Bensch, 2021; Tau and Peterson, 2010): primary neurulation (neural tube formation), neuronal proliferation (neurogenesis), neuronal migration and formation of cortical cell layers, synaptogenesis, pruning (elimination of synapses) and apoptosis, myelination, and cortical thinning. The first trimester of pregnancy and late adolescence represents two critical periods of susceptibility to schizophrenia due to the influence of risk factors on cell proliferation and synapse elimination (Catts et al., 2013; Selemon and Zecevic, 2015)

Neuroplasticity (neural plasticity, brain plasticity) is the ability of the brain to change its structure, function, and activity in response to external and internal stimuli during normal and pathological neurodevelopment throughout life. It ensures the development, growth, and reorganization of the developing and adult brain. The term neuroplasticity includes synaptic plasticity, nonsynaptic (structural) plasticity, and neurogenesis. Synaptic plasticity is realized by changing the strength of synapses. Nonsynaptic plasticity is mediated by changes in neuronal structures such as the soma, axon, or dendrites (Citri and Malenka, 2008).

Neurochemistry of psychotic disorders involves the activity of signaling pathways associated with neurotransmitter receptors with an impact on the prefrontal cortex. At the molecular level, the transmission and processing of information mediated by neurotransmitters and growth factors and their receptors and transporters is disrupted in schizophrenia. Various brain circuits and neurotransmitter systems participate in schizophrenia, especially dopamine, glutamate, γ-aminobutyric acid (GABA) and serotonin (Fallon et al., 2003).

Antipsychotic medication is used to treat psychotic symptoms in schizophrenia and schizoaffective disorder. Knowledge of the molecular and cellular mechanisms of action of drugs used to manage psychotic symptoms (antipsychotics) is one of the main sources of knowledge about the biological nature of schizophrenia and is reflected in the biological hypotheses of schizophrenia. All approved antipsychotics target the dopaminergic system and thus support the dopamine hypothesis. Novel treatment targets beyond the dopamine hypothesis include glutamate, serotonin, acetylcholine, γ-aminobutyric acid (GABA), and cannabinoid systems, mitochondrial function, and components of neuroinflammatory and oxidative stress pathways (Ľupták et al., 2021b; Sethi et al., 2019; Yang and Tsai, 2017). Understanding the interactions of monoaminergic systems, glutamate transmission in the prefrontal cortex, mitochondrial dysfunction, and trace amine-associated receptor 1 activation in modulating brain functions may be an interesting insight into the pathophysiology and treatment of schizophrenia (Dodd et al., 2021; Rutigliano et al., 2018). Due to the role of epigenetic changes in neurodevelopmental diseases, regulation of DNA methylation and histone acetylation could be effective interventions in the development of schizophrenia (Richetto and Meyer, 2021). However, sufficiently specific regulators of epigenetic processes without side effects have not yet been found (Hannon et al., 2016b; Jaffe et al., 2016; Mastrototaro et al., 2017; Reichard and Zimmer-Bensch, 2021; Smigielski et al., 2020). A promising target for the diagnosis and treatment of schizophrenia is the regulation of bioenergetics and transport, including vesicle transport. Schizophrenia hypotheses often specify the molecular targets of new potential antipsychotics, and conversely, knowledge of the mechanism of action of existing and new antipsychotics contributes to the confirmation or modification of some hypotheses.

This review summarizes the main viable biological hypotheses of schizophrenia based on current knowledge of risk factors and biomarkers, and mechanisms of action of antipsychotics or psychotomimetics, with a focus on neurochemical and integrative models (Supplementary Table S1). The main rationale of this review is to contribute to the discussion of current concepts of schizophrenia (Tandon et al., 2022) by summarizing valid etiological, neurodevelopmental, and biological hypotheses and updating historical perspectives on the etiology of schizophrenia. Emphasis is placed on the integration of different research approaches, reflecting the fact that different internal and external stimuli can lead to the same disease symptoms.

2. Risk factors and biomarkers of schizophrenia

This chapter briefly summarizes, with references to corresponding reviews, analyses, and meta-analyses, information on risk factors and genetic, epigenetic, nongenetic, neuroimmunological, neurophysiological, and neuroimaging biomarkers of schizophrenia. Finally, the necessity and perspective of biomarkers measurable in peripheral blood are discussed. In the following chapters, biomarkers are presented in the context of the presented hypotheses.

Risk factors of schizophrenia include biological (genetic factors, prenatal and perinatal events, drug abuse, and disturbed neurodevelopment and neurotransmission) and environmental/social (urban residence, migration, and childhood and adult adversity) factors (Stilo and Murray, 2010, 2019).

Biomarkers are expected to estimate the risk of developing schizophrenia and/or predict the clinical course of the disease A topic of interest is finding reliable biomarkers for the early detection of schizophrenia that can be measured in the brain, cerebrospinal fluid (CSF), or blood. Knowledge of risk factors and biomarkers associated with specific disturbances in neurodevelopment, neuroplasticity, and brain chemistry, including structural and functional brain changes measurable using neuroimaging methods, is important for the

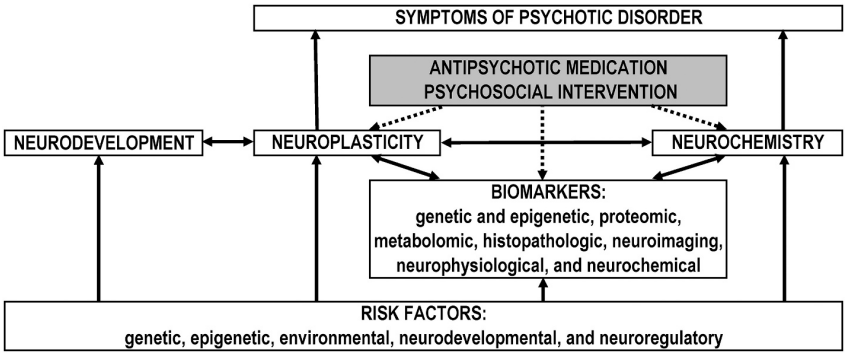

Fig. 1. Scheme of the underlying processes and concepts in the development of psychotic disorders showing that different risk factors and biomarkers may converge on molecular pathways responsible for disease symptoms. Arrows indicate the interconnection of processes and parameters, and double-headed arrows indicate that biomarkers include measurable indicators of neurodevelopment, neuroplasticity, and neurochemistry.

formulation of biological hypotheses of schizophrenia. Genetic (Tamminga et al., 2017), epigenetic (Hannon et al., 2021; Richetto and Meyer, 2021), proteomic (Rodrigues et al., 2022), metabolomic (Cao et al., 2020), neurochemical (Reynolds, 2022), neurophysiological (Kim et al., 2020), histopathological (Raabe et al., 2019), and neuroimaging (Kraguljac et al., 2021) techniques have been used to search for biological markers of schizophrenia. Non-invasive *in vivo* measurements in the brain are made possible by neuroimaging methods. New findings are mainly brought by positron emission tomography (PET) and single-photon emission computed tomography (SPECT) (Cumming et al., 2021), but their use is limited by low resolution and the need to synthesize suitable tracers.

The **genetic** component of schizophrenia is high. The heritability of schizophrenia is about 79% (Hilker et al., 2018), with a shared influence of the environment of 11% (Sullivan et al., 2003; Tandon et al., 2008). The Psychiatric Genomics Consortium (http://pgc.unc.edu) reported a systematic analysis of schizophrenia data in a multistage genome-wide association study (GWAS) (Schizophrenia Working Group of the Psychiatric Genomics, 2014). The study resulted in the identification of 128 independent associations spanning 108 conservatively defined loci with genome-wide significance, and this number continues to rise. Thus, genes for schizophrenia have been found. However, the identified loci do not directly imply the involvement of specific genes and explain only a small part of the hereditary risk (Le and Stein, 2019; So et al., 2011). It has been estimated that only 23% of variations in schizophrenia can be attributed to common variants; 77% of genetic variation can be caused by rare variants (Lee et al., 2012).

Attention is given to the role of **epigenetic** changes in mental disorders (Richetto and Meyer, 2021; Smigielski et al., 2020; Snyder and Gao, 2013). Epigenetic processes (such as DNA methylation, histone modifications, chromatin remodeling, and microRNA expression) are reversible, flexible, and can respond rapidly to environmental changes and other stimuli. Accumulated evidence suggests that epigenetic modifications mediate gene-environment interactions by regulating gene expression and play an important role in the development and progression of many common diseases, including schizophrenia (Jin and Liu, 2018; Smigielski et al., 2020). Schizophrenia is thought to be the result of interactions between genetic predisposition and environmental influences, with regulation at the level of epigenetic changes (Harrison, 2015). Epigenetic changes in schizophrenia are studied primarily in terms of how they contribute to the hypofunction of *N*-methyl-D-aspartate (NMDA) receptors via changes in the expression levels of genes for NMDA receptors (Snyder and Gao, 2020) or how they regulate the immune response and neuroinflammatory processes by altering the gene expression of proinflammatory cytokines (Alam et al., 2017; Müller, 2018).

An umbrella review of meta-analyses of **nongenetic** peripheral biomarkers for schizophrenia has shown that suitable candidates for peripheral biomarkers include adiponectin, anti-gliadin IgA, arachidonic acid, cortisol, folate, malondialdehyde, nerve growth factor, NMDA receptor antibody seropositivity, and soluble interleukin 2 (IL2) receptor. Highly significant evidence exists for decreased serum folate and pyridoxal (vitamin B6) deficiency in schizophrenia compared to controls (Carvalho et al., 2020; Tomioka et al., 2018). Oxytocin, which is known to regulate emotional responses and prosocial behavior, is significantly reduced in schizophrenia (Ferreira and de Lima Osorio, 2022) and regulates various symptoms of schizophrenia (Goh et al., 2021). In schizophrenia, increased superoxide dismutase, increased malondialdehyde, increased activity of nuclear factor kappa B, inactivation, or downregulation of the thioredoxin and glutathione systems, and downregulation of the nuclear factor erythroid 2-related factor (Nrf2) system have been observed. Thus, the pathological effects of nitrosative and oxidative stress and mitochondrial dysfunction are multifactorial (Morris et al., 2020).

Several candidate biomarkers have provided **neuroimmunological** research in testing the hypothesis that immune dysfunction may be involved in the pathophysiology of schizophrenia (Notter, 2018). Higher levels of both pro-inflammatory and anti-inflammatory cytokines were confirmed in the peripheral blood (Goldsmith et al., 2016). In CSF, a meta-analysis confirmed higher levels of pro-inflammatory cytokines and lower levels of anti-inflammatory cytokines in schizophrenia (Wang and Miller, 2018). Potential biomarkers of schizophrenia measurable in peripheral blood include changes in inflammatory-related cytokine levels, such as IL1 (or its receptor antagonist), soluble IL2 receptor, IL4, IL6, IL8, and tumor necrosis factor-α (TNF-α) (Miller et al., 2011; Misiak et al., 2021; Na et al., 2014; Trovao et al., 2019; Zhou et al., 2021). A meta-analysis of oxidative and inflammatory markers confirmed lower total antioxidant status, lower levels of docosahexaenoic acid and higher levels of homocysteine, IL6, and TNF-α in patients with a first episode of the disease (Fraguas et al., 2019). Both genetic and epigenetic studies support the immunopathogenetic basis of schizophrenia (Avramopoulos et al., 2015; Liu et al., 2014). It has not yet been confirmed whether inflammatory biomarkers are state or trait indicators of psychotic illness (Khoury and Nasrallah, 2018).

Proposed candidate **neurophysiological** endophenotypes in schizophrenia include P50 event-related potential amplitudes and gating, mismatch negativity, P300 event-related potential, and oculomotor antisaccade. Most neurophysiological and neurocognitive measures show deficits in patients, substantial heredity, reliability of repeat tests, and time stability (Light et al., 2015; Owens et al., 2016). However, there is currently no convincing evidence of an association between any single-nucleotide polymorphism and any electrophysiological intermediate phenotype (Hederih et al., 2021).

Neuroimaging techniques have confirmed certain neuroanatomical changes in schizophrenia, such as reductions in the volume of the whole brain and gray matter, an increase in the volume of the ventricles, or a reduction in the structures formed by the white matter (Garey, 2010; Harrison et al., 2003; Sommer and Kahn, 2015). Functional changes, especially reduced metabolism in the prefrontal cortex (hypofrontality), can be related to the observed structural abnormalities (Weinberger and Berman, 1988). Unfortunately, hypofrontality is not specific for schizophrenia. Functional neuroimaging studies have confirmed that structural changes in the brain are accompanied by functional changes (Gao et al., 2018). At the microanatomical level, consistent observations include a decrease in the size of neurons accompanied by decreased branching of dendrites and axons (Fatemi et al., 2001; Vawter et al., 2002) and alterations of neuron density.

Abnormalities in both early brain development (before or around birth) and late development (prior or around the onset of symptoms) have been proposed (Weinberger, 1987). Neuroimaging studies have confirmed that brain structure abnormalities in schizophrenia include the smaller hippocampus, amygdala, thalamus, nucleus accumbens and intracranial volumes, and larger pallidum and lateral ventricles (van Erp et al., 2016; van Erp et al., 2018). Many regional differences have been identified in human gray matter, including decreased cortical gray matter volume in the dorsolateral prefrontal cortex (DLPFC), cingulate gyrus, medial temporal lobe, and superior temporal gyrus (Haijma et al., 2013; van Erp et al., 2018; Yamasue et al., 2004). The most significant cortical thinning was in the frontal and temporal areas of the brain. The characteristic decrease in gray matter in schizophrenia is more pronounced on the left side of the brain (Glahn et al., 2008). Reduced insula volume and thickness were associated with positive, negative, and cognitive symptoms of psychosis. (Sheffield et al., 2021). A meta-analysis of structural and functional neuroimaging studies of the whole brain did not show significant changes after correction for multiple comparisons (Luna et al., 2022). At the cellular level, there is a deficiency of GABA interneurons.

Diffusion-weighted imaging studies have revealed impaired white matter morphology and integrity in schizophrenia (Wheeler and Voineskos, 2014). It is thought that changes in the development and structure of white matter may contribute to the development of schizophrenia (Duchatel et al., 2019).

Changes in brain structure, function, and neurochemistry are not very regionally specific in schizophrenia, but are more pronounced in the association (prefrontal, parietal, and temporal) cortex and in the subcortical (limbic, striatal) areas of the brain. Due to the large interindividual differences, these abnormalities are not specific enough to allow the diagnosis of the schizophrenia but may facilitate the prediction of outcome and treatment response (Keshavan et al., 2020b). Some peripheral biomarkers of schizophrenia are common with schizoaffective and bipolar disorder; the sharing of biological factors responsible for the symptoms of these diseases suggests a possible continuum in their etiology, which may contribute to understanding the pathophysiology of schizophrenia (Birur et al., 2017; Sigitova et al., 2017; Yamada et al., 2020).

Reliable biomarkers with sufficient sensitivity and specificity have not yet been found to explain the pathophysiology of schizophrenia and for use in clinical practice (Schmitt et al., 2017; Schmitt et al., 2016). The main limitation in finding biomarkers of schizophrenia is the unavailability of brain tissue. For the applicability of peripheral biomarkers in CSF and especially in peripheral blood, evidence of their close connection with changes in the brain is essential. From this point of view, suitable biomarkers should be those that pass through the blood-brain barrier or are transported from the brain to the periphery, e.g., by means of brain-derived exosomes. Exosomes were recognized as structures that allow intercellular and interstitial transport of molecules. Brain-derived exosomes can transport a number of proteins, lipids, DNA, and RNAs associated with schizophrenia across the blood-brain barrier (Du et al., 2021; Ranganathan et al., 2022; Saint-Pol et al., 2020; Singh et al., 2022). Thus, the study of peripheral biomarkers of schizophrenia seems promising.

3. Environmental approach to schizophrenia hypotheses

Schizophrenia is caused by interactions between genetic predisposition and environmental risk factors. In this chapter, hypotheses emphasizing the influence of the environment, especially stress, on the development of schizophrenia are presented.

The effect of stress in various stages of schizophrenia has long been described; however, this is not a clear cause of the disease and its repeated episodes. The **vulnerability-stress model** of schizophrenia was formulated in 1977 (Zubin and Spring, 1977) and followed the concept of vulnerability to neurosis proposed in 1944 (Slater and Slater, 1944). According to this model, a psychotic episode can develop if the stress exceeds a certain vulnerability threshold. Note that the interaction of genetic and environmental stimuli appears to be essential in the development of schizophrenia (Brown, 2011).

It can be hypothesized that with an altered homeostatic state (new homeostatic setpoint), stress responses and some physiological mechanisms not related to stress (e.g., chronobiological changes and bioenergetic or metabolic changes associated with altered enzyme activities, substrate availability, or normal aging) can cause imbalances in brain neurotransmission resulting in the development of recurrent episodes of mental illness, such as schizophrenia. **Hypothesis of an imbalance in homeostatic signaling** (Landek-Salgado et al., 2016) proposes that inflammatory processes, oxidative stress, and disrupted endocrine and metabolic homeostatic signaling cascades that mediate pathological modulation of neurotransmission and myelinated tracks are responsible, at least in part, for deficits in neural connectivity associated with white matter in schizophrenia. Stress signaling can be involved in changes in neurotransmission and connectivity, and conversely, disturbances in neurotransmission and neural connectivity can activate stress signaling.

The cumulative effects of stress, quantified as allostatic load, could be increased in schizophrenia. Repeated “hits,” lack of adaptation, prolonged response, and inadequate response lead to allostatic load (Juster et al., 2011; McEwen, 2006). The allostatic load score determined using a set of biomarkers was significantly increased in schizophrenia spectrum disorder patients with both early psychosis and a chronic disease course (Guidi et al., 2021; Savransky et al., 2018). Dysregulation of physiological functions captured by the allostatic load index appears to occur in subjects at familial risk of psychosis, and progression occurs when psychosis worsens (Piotrowski et al., 2019). However, due to large interindividual differences in schizophrenia patients and age-matched healthy controls (Nugent et al., 2015), the allostatic load score is not of diagnostic value *per se*. The allostatic load, which represents systemic biological dysregulations in response to repeated or chronic stress, may participate in the pathophysiology of bipolar disorder and schizophrenia (Berger et al., 2009; Piotrowski et al., 2019; Sigitova et al., 2017). The increase in allostatic load confirms the hypothesis that stress-related pathophysiology may contribute to the onset of schizophrenia; however, it is not a necessary or sufficient condition for the onset of symptoms of the disease and the expression of other biomarkers of schizophrenia. The association of allostatic load with altered homeostatic processes must be further studied to contribute to the explanation of the pathophysiology of schizophrenia.

Viral infections have been studied as a stress factor capable of inducing schizophrenia through disruption of neurodevelopment. According to the **viral model** of schizophrenia, prenatal viral or bacterial infections and inflammation may be a significant risk for the later development of schizophrenia (Kneeland and Fatemi, 2013). However, evidence for maternal influenza during pregnancy as a risk factor for schizophrenia is insufficient (Selten and Termorshuizen, 2017).

Epidemiological data indicate that environmental risk factors for schizophrenia include several prenatal and perinatal complications (Costas-Carrera et al., 2020; Davies et al., 2020), the use of cannabis (tetrahydrocannabinol can cause psychosis and schizophrenia in at-risk populations) (Patel et al., 2020), childhood trauma (Setien-Suero et al., 2020), social stressors (Susser and Patel, 2014), malnutrition leading to maternal vitamin D deficiency (Cui et al., 2021; Lisi et al., 2020) or to low folate and high homocysteine (Picker and Coyle, 2005), infection with influenza virus (Fatemi et al., 2012) and human endogenous retroviruses (Balestrieri et al., 2019), lower premorbid intelligence quotient (Schulz et al., 2014), and drug abuse (Ham et al., 2017). Only a history of obstetric complications, stressful events, childhood adverse events, cannabis use, and serum folate levels have provided reliable evidence of an association with schizophrenia (Belbasis et al., 2018).

4. Genetic and epigenetic models of schizophrenia

Genetic variants and epigenetic changes are important risk factors in the etiopathogenesis of schizophrenia (Henriksen et al., 2017). Genetic hypotheses also include mitochondrial DNA damage, epigenetic hypotheses include the role of noncoding RNAs.

Genetic models conceive of schizophrenia as a genetic disorder of the synapses and cortical microcircuits (Harrison and Weinberger, 2005), i.e., they assume that changes in neurotransmission, neuroplasticity and synaptogenesis in schizophrenia are largely genetically determined. Attention is given to genetically and epigenetically determined changes in glutamatergic, dopaminergic, and GABAergic activities. Note, that schizophrenia partially shares a common genetic etiology with bipolar disorder (de Sousa et al., 2021; Kato, 2007; Kloiber et al., 2020; Lichtenstein et al., 2009). A combined GWAS of bipolar disorder and schizophrenia cases versus controls identified a polygenic signal capable of distinguishing schizophrenia from bipolar disorder (Ruderfer et al., 2014).

The risk of developing schizophrenia is associated with a polygenic risk score, family psychiatric history, and socioeconomic status (Agerbo et al., 2015). Genetic epidemiological studies show a lifetime risk of developing schizophrenia in the general population of 0.5–1% and a significantly higher risk of schizophrenia occurs in the family (McGrath et al., 2008; Saha et al., 2005). Twin studies have been important in the quantification of genetic contributions to the etiology of schizophrenia; the risk of illness in the cotwin of a proband-twin of 41-65% in

monozygotic pairs and 0-28% in dizygotic pairs was found (Cardno and Gottesman, 2000). However, since DNA is not the sole agent of inheritance, estimates of the genetic contribution to schizophrenia based on twin studies may not be accurate (Charney, 2012). Somatic mutations appear to contribute to the development of schizophrenia (Nishioka et al., 2018).

Based on GWAS, the **dysregulated glycosylation hypothesis** that common genetic variants alter glycosylation of some schizophrenia-associated proteins, such as dopamine and glutamate receptors, voltage-gated calcium channels, and complement-associated proteins, has been formulated (Mealer et al., 2020; Mealer et al., 2022).

Mutations, polymorphisms, and deletions of **mitochondrial DNA** (mtDNA), which can cause mitochondrial dysfunction, are also involved in the pathophysiology of schizophrenia, especially apoptosis and inflammatory responses. Deficiencies in the expression of various mitochondrial genes have been found in schizophrenia, including those involved in the function of the citric acid cycle and regulation of the mitochondrial energy metabolism and reactive oxygen species (ROS) production (Roberts, 2021). An increase in circulating cell-free mtDNA fragments and mitochondrial dysfunction have been observed in schizophrenia (Suarez-Mendez et al., 2020).

The **epigenetic hypothesis** of schizophrenia posits that interactions between environmental factors and genetically and epigenetically determined susceptibility to schizophrenia are responsible for the pathogenesis of the disease. The hypothesis proposes that epigenetic changes disrupt the cortical transcription of GABA neurons, affecting both GABAergic signaling via presynaptic GABA release and glutamatergic signaling at the level of postsynaptic hypofunction (Grayson, 2010). This hypothesis includes a deficit of both GABA neurons and a glutamatergic deficit. Inhibitory GABA interneurons modulate the excitability of pyramidal and other neurons, which leads, for example, to disruption of the synchronization of pyramidal neuron firing (Lewis et al., 2005). Reduced activity of glutamate NMDA receptors on GABA interneurons causes glutamatergic hypofunction and leads to insufficient GABA release onto cortical pyramidal neurons.

It is hypothesized that neurodevelopmental changes in the prefrontal cortex associated with schizophrenia may be linked to prenatal stress-induced epigenetic changes in the reelin gene (Guidotti et al., 2000; Negron-Oyarzo et al., 2016). The best characterized epigenetic modification that affects gene expression is histone acetylation and methylation and DNA methylation (Roth et al., 2009; Thomas, 2017). Changes in histone acetylation and methylation can affect the transcription of genes involved in the differentiation and myelination of oligodendrocytes and thus cause oligodendroglia abnormalities (deficiency of oligodendrocytes and myelin) (Li et al., 2022). Meta-analyses of epigenome-wide association studies (EWAS) have supported a role for differential DNA methylation in schizophrenia (Hannon et al., 2016a; Hannon et al., 2021), but it is unclear whether differences in methylation are directly disease-related or due to other schizophrenia-related factors (e.g. effects of antipsychotics, stressful life, diet, and comorbid diseases). It was concluded that although these DNA methylation differences are unlikely to be mechanistically related to neuropathological changes in the brain, they can be used as prognostic biomarkers in individuals with first-episode psychosis and potentially to differentiate individuals with treatment-resistant schizophrenia.

Because the role of **noncoding RNAs** in brain development, neuroplasticity, and stress response has been confirmed, long noncoding RNAs and microRNAs can affect the development of neuropsychiatric diseases such as schizophrenia (Du et al., 2019; Yoshino and Dwivedi, 2020). For example, microRNA-137 and its target gene networks are associated with schizophrenia (Sakamoto and Crowley, 2018). Circular RNAs are non-coding RNAs that are involved in the regulation of gene expression, neuroplasticity and cognition, and changes in their concentrations are associated with schizophrenia (Li et al., 2020; Mahmoudi et al., 2019; Mahmoudi et al., 2021). Exosomal circular RNAs are stable and can be transported across the blood-brain barrier (Li et al., 2015), making them a promising biomarker of schizophrenia (Tan et al., 2021).

5. Neurodevelopmental and dysplastic approaches to schizophrenia hypotheses

A neurodevelopmental approach to schizophrenia includes the influence of both genetic and environmental factors. In connection with a number of findings about schizophrenia, the general neurodevelopmental hypothesis is refined into hypotheses focused on certain aspects, causes, and manifestations of impaired neurodevelopment, such as abnormal structure and function of cell membranes, impaired development of neural circuits, excessive synaptic pruning, reduced neuropil, altered aging process, and multifactorial vulnerability. A dysplastic approach is often discussed, which includes impaired neuroplasticity of certain brain circuits, insufficient metaplastic regulation in perceptual, cognitive, and motor systems, local brain abnormalities and abnormal synaptic connections, consequences of increased activity of neurotrophins, and pathology of the prefrontal cortex.

The **neurodevelopmental model** of schizophrenia is based on clinical, epidemiological, genetic, and brain imaging studies (McGrath et al., 2003; Piper et al., 2012) and assumes that the increased risk of developing schizophrenia is due to abnormal brain development caused by genetic and environmental factors many years before the onset of the disease (Murray and Lewis, 1987; Owen et al., 2011; Rapoport et al., 2005; Rapoport et al., 2012; Weinberger, 1987).

Normal cortical development includes brain cell proliferation and migration, myelination, and circuit formation during prenatal life and during the first two postnatal decades (Reichard and Zimmer-Bensch, 2021). Possible neurodevelopmental mechanisms for schizophrenia probably include decreased myelination and altered excitatory-inhibitory balance in the prefrontal cortex (due to reduced formation of inhibitory neurotransmitter pathways and excessive excitatory pathway pruning) (Insel, 2010).

Due to the important role of phospholipids in brain development, the **membrane phospholipid hypothesis** of schizophrenia has been formulated (Horrobin, 1998; Horrobin et al., 1994), according to which the biochemical basis for the neurodevelopmental concept of schizophrenia lies in abnormalities of membrane biochemistry and structure. This hypothesis was supported by the detection of aberrations in essential fatty acid levels in peripheral blood patients with schizophrenia, dysregulation of essential fatty acid metabolism in people at risk of psychosis, decreased metabolism of glycerophosphoinositols and cardiolipins in the prefrontal cortex (Yu et al., 2020), increased lipid peroxidation (Kuloglu et al., 2002), and downregulation of some fatty acids in the blood exosomes of patients with schizophrenia (Du et al., 2021).

Different types of neurodevelopmental models of schizophrenia have been included in the **unitary pathophysiological hypothesis** (Keshavan, 1999), according to which early brain insults can lead to abnormal development of certain neural circuits, which can lead to cognitive and psychosocial dysfunction. This 'three hit' model integrates (i) early neurodevelopmental changes (caused by genetic and environmental insults and glutamatergic neuronal loss in pregnancy), (ii) late neurodevelopmental changes (associated with hypofunction of NMDA receptors and excessive elimination of synapses in adolescence), and (iii) possible neurodegenerative processes (glutamate excitotoxicity and oxidative stress accompanying the untreated phase of the disease). Excessive elimination of synapses followed by dopaminergic hyperactivity may lead to the onset of schizophrenia in adolescence; decreased glutamatergic neurotransmission may predetermine these processes.

The neurodevelopmental hypothesis of schizophrenia includes anatomical changes in the brain, genetics, environmental factors, and gene-environment interactions (Fatemi and Folsom, 2009). The **synaptic pruning hypothesis** of schizophrenia (Feinberg, 1982; Keshavan et al., 1994; Lewis, 2009) explains the onset of schizophrenia during adolescence and young adulthood by excessive synaptic pruning and

disturbed neuroplasticity at this age. The hypothesis is related to the view that the onset of schizophrenia in adolescence may be associated with synaptic or axonal pruning, but not with neuronal cell death. The **reduced neuropil hypothesis** has been proposed to explain macroscopic changes of the cerebral cortex in schizophrenia, increased cell density, and changes in synaptic and dendritic architecture (Selemon and Goldman-Rakic, 1999). The time-dependent reduction in brain volume in schizophrenia can be explained by this hypothesis, but the hypothesis has not been adequately tested (Bakhshi and Chance, 2015). GWAS found a high risk of developing schizophrenia associated with variation in the major histocompatibility complex locus (Schizophrenia Working Group of the Psychiatric Genomics, 2014). This association arises in part from alleles of the complement component four genes causing excessive complement activity in the development of schizophrenia (Sekar et al., 2016). Microglia-mediated complement abnormalities may be a mechanism by which excessive pruning of synapses occurs during the onset of schizophrenia (Keshavan et al., 2020a).

Based on a summary of schizophrenia risk factors, a **multiple hit theory** of schizophrenia has been proposed (Davis et al., 2016), according to which schizophrenia is a process involving multiple vulnerability factors across many neurodevelopmental windows ("hits" in the prenatal period, in childhood, adolescence and adulthood). Genetic vulnerability in interactions with environmental influences, such as prenatal vitamin D, nutrition, childhood trauma, viral infections, smoking, cannabis use, intelligence quotient, and social defeat, controls the development of schizophrenia. The neurodevelopmental phase involves changes in synaptogenesis, synaptic plasticity, and myelination.

Neuroanatomical studies (altered neuroplasticity, impaired cortical inhibitory function, and abnormal brain aging processes) support a **progressive neurodevelopmental model** of schizophrenia that assumes that the onset of schizophrenia is preceded by changes in neurodevelopment that are affected by maturation processes; later regulation of neuroplastic processes differs from healthy aging, i.e., there is an altered aging process associated with ongoing abnormal neuroplasticity (Bakhshi and Chance, 2015).

To combine the genetic, environmental, and neurodevelopmental features of schizophrenia with the symptoms of the disease and the effects of psychotomimetics and antipsychotics, the concept of impaired neuroplasticity was adopted early and subsequently developed (Friston et al., 2016; Friston, 1998; Guterman et al., 2021; Haracz, 1985; Keshavan et al., 2015; Port and Seybold, 1995). According to the **dysplastic model** of schizophrenia, cognitive and deficit symptoms may be due to impaired plasticity of certain brain circuits, which may lead to aberrant plasticity of other neural circuits, leading to affective symptoms and ultimately to psychosis (Keshavan et al., 2015). The **imbalanced plasticity hypothesis** has been proposed (Guterman et al., 2021), which assumes that psychotic symptoms in schizophrenia are the result of insufficient metaplastic regulation in perceptual, cognitive, and motor systems. This hypothesis is based on the key roles of long- and short-term synaptic plasticity in the learning and inference processes.

The **disconnection hypothesis** (Friston, 1998, 1999) assumes that the pathophysiology of schizophrenia is due to local brain abnormalities and abnormal synaptic connections leading to abnormal or ineffective communication between functional areas of the brain. The hypothesis focuses on changes at the level of modulation of associative changes in synaptic efficacy in the brain systems that are responsible for learning, memory, and emotion. The disconnection hypothesis conceives of schizophrenia as a consequence of specific damage to the structural and synaptic plasticity of the brain, with synaptic plasticity being responsible for the onset of the symptoms of the disease. This explains both the rapid onset of psychotomimetic-induced psychotic symptoms and the onset of symptoms of schizophrenia in adolescence due to abnormal modulation of experience-dependent synaptic plasticity (Friston, 2002). Recently, the disconnection hypothesis attempted to establish a link between the symptoms of schizophrenia and the pathophysiology associated with the effect of modulating neurotransmitters on synaptic efficacy mediated by glutamate NMDA receptors (Friston et al., 2016). A new extension of the neurodevelopmental model of schizophrenia has been proposed, according to which etiology of schizophrenia is based on the abnormal formation and maturation of connectome leading to manifestations of the symptoms of schizophrenia (Collin and Keshavan, 2018; Demro et al., 2021).

There is evidence for the **neurotrophin hypothesis**, which proposes that repetitive neuronal activity increases the expression, secretion, and activity of neurotrophins, leading to modification of synaptic plasticity and connectivity in schizophrenia (Lang et al., 2004). According to this hypothesis neurotrophins (mainly brain-derived neurotrophic factor (BDNF), nerve growth factor, and neurotrophin-3) are involved in the pathophysiology of schizophrenia, and alterations in the expression of neurotrophins could be responsible for disturbed neurodevelopment and neuroplasticity associated with schizophrenia (Durany et al., 2001). The hypothesis is supported both by changes in neurotrophin concentrations in the periphery in schizophrenia (Ajami et al., 2014; Rodrigues-Amorim et al., 2018) and by a significant association between the BDNF gene Val66Met polymorphism and schizophrenia (Kheirollahi et al., 2016).

The hypothesis that **inhibitory cortical circuits** are involved in the development of schizophrenia was formulated based on the observation that impairment of some cognitive functions in schizophrenia are associated with decreased GABA synthesis in a subpopulation of parvalbumin-expressing inhibitory GABA neurons located in the dorsolateral prefrontal cortex (Lewis et al., 2005). Evidence for this hypothesis is provided by both *in vivo* neuroimaging studies and postmortem studies of GABA neurotransmission in the prefrontal cortex and other cortical areas in schizophrenia (Dienel and Lewis, 2019).

The mechanism of **prefrontal cortex pathology** in schizophrenia has been proposed, including changes in neuroplasticity, neuroinflammation, and oxidative and nitrosative stress (Tendilla-Beltrán et al., 2021). According to this model, impaired structural and functional plasticity of prefrontal cortex pyramidal cells in schizophrenia is associated with decreased dendritic spine density and impaired synaptic activity (especially glutamate and GABA neurotransmission) regulated by neurotrophic factors such as BDNF and neuregulin 1. Altered GABAergic neurotransmission, and consequently excitatory-inhibitory coupling in the prefrontal cortex, is due to impaired synthesis, release, and reuptake of GABA, as well as loss of GABA interneurons positive for the calcium-binding protein parvalbumin, which may be due to oxidative and nitrosative stress. These processes are conditioned by oxidative and nitrosative stress, which can be enhanced by decreased antioxidant protection (regulated by perineuronal nets and transcription factor Nrf2) and microglia and astrocyte hyperactivity.

6. Neurochemical approach to schizophrenia hypotheses

The basic neurochemical hypotheses of schizophrenia include the dopamine, glutamate, and serotonin hypotheses (Stahl, 2018). These hypotheses encompass the interconnection of all three neurotransmitter systems so that they can be combined into one neurochemical hypothesis, which reflects that schizophrenia is a heterogeneous group of disorders with mixed pathophysiology. The role of the purinergic and endocannabinoid system in the pathophysiology of schizophrenia is currently being studied and included in neurochemical schizophrenia hypotheses.

6.1. Dopamine hypothesis

The original dopamine hypothesis of schizophrenia was based primarily on the finding that effective antipsychotics block dopamine receptors in the brain (van Rossum, 1966). According to the **classical (receptor) dopamine hypothesis** of schizophrenia, psychotic symptoms are associated with dopaminergic hyperactivity in specific areas of the brain, especially with increased activity of dopamine D_2 receptors (Carlsson, 1988; Meltzer and Stahl, 1976; Snyder, 1976). It was only

much later confirmed that excessive dopamine activity may be presynaptic due to excessive dopamine release or postsynaptic due to increased density or sensitivity of D_2 receptors (Abi-Dargham et al., 2000; Howes et al., 2015). Overactivation of D_2 receptors is part of the overall dysregulation of synaptic signal transduction in schizophrenia. Thus, the dopamine hypothesis does not assume that dopamine hyperactivity fully explains the symptoms of schizophrenia.

According to the **modified dopamine hypothesis**, schizophrenia is characterized by abnormally low prefrontal dopamine activity (negative symptoms are caused by frontal hypodopaminergia), leading to excessive dopamine activity in mesolimbic dopamine neurons (positive symptoms are caused by striatal hyperdopaminergia). The cooccurrence of high and low dopamine activity in different neural circuits may explain the coexistence of negative and positive symptoms of schizophrenia (Davis et al., 1991). A subcortical/cortical imbalances and the involvement of several other neurotransmitters in the pathophysiology of schizophrenia are thought (Carlsson et al., 2000). The hypothesis was formulated based on the observation that (i) that dopamine concentrations and dopamine receptors activity in various subcortical areas in the brains of schizophrenic patients are increased, (ii) antipsychotics act by reducing dopamine activity in mesolimbic dopamine neurons, and (iii) negative symptoms of schizophrenia are associated with decreased dopamine activity in the prefrontal cortex, with prefrontal dopamine neurons inhibiting subcortical dopamine activity.

The unifying dopamine hypothesis of schizophrenia, the so-called **final common pathway**, assumes that striatal dopamine dysregulation and altered transmission of nerve signals resulting from the interaction of various environmental, genetic, and neurodevelopmental risk factors, lead to psychosis (Howes and Kapur, 2009). The hypothesis was formulated primarily on confirmed environmental and genetic risk factors and based on evidence from neuroimaging studies. This hypothesis does not focus on the dopamine system but combines risk factors for schizophrenia with increased presynaptic striatal dopaminergic function and other brain functions that underlie negative and cognitive symptoms. It explains how frontotemporal structural and functional abnormalities and cognitive disorders can converge neurochemically and cause psychosis.

The **integrated sociodevelopmental-cognitive model** (Howes and Murray, 2014) assumes that anomalous neurodevelopment caused by genes or neurodevelopmental hazards and childhood adversity sensitizes the dopamine system and results in excessive presynaptic dopamine synthesis and release. Subsequent acute psychosocial stress results in dysregulated dopamine release, aberrant processing of stimuli, and symptoms of schizophrenia (which in turn cause further stress). The increased sensitivity of the dopamine system to acute psychosocial stress (due to risk factors-induced impairment of glutamatergic regulation) is thought to lead to increased striatal dopamine release and disease symptoms (Howes et al., 2017).

A **model for a "dual hit" on dopamine function** in schizophrenia has been proposed (Abi-Dargham, 2017; Guerrin et al., 2021), according to which (1) genetic vulnerability (including D_2 genes and other genes related to the dopamine system and synapse strength) may affect the developmental trajectories of the brain and various neural circuits; and (2) environmental factors (e.g., stress, drugs, urbanity, diet, and inflammation) can exacerbate the genetic bias through the release of dopamine, further augmenting abnormal D_2 activity, circuit development, and connectivity. The model was supported by a new topography of dopaminergic dysregulation in schizophrenia (Weinstein et al., 2017) and the finding that striatal-cortical disconnection may underlie the effects of dopamine dysregulation on the onset of symptoms of schizophrenia (Horga et al., 2016).

The hypothesis that psychosis is caused by excessive activity in the mesolimbic dopamine pathway was supported by imaging data showing early dysregulation in the striatum, manifested as excessive dopamine synthesis and release (Howes et al., 2012). Advances in neuroimaging techniques have led to the finding that dopaminergic dysfunction in schizophrenia is greatest in the nigrostriatal pathways, indicating an important role for the dorsal striatum in the pathophysiology of schizophrenia (McCutcheon et al., 2019). Data show dopamine deficits in most cortical areas, even in other extrastriatal subcortical regions (Slifstein et al., 2015). However, postsynaptic receptors and transporters do not show reliably detectable altered expression in either the striatal or extrastriatal areas of the brain in schizophrenia (Weinstein et al., 2017).

There are several lines of evidence for the dopamine hypothesis. (1) Drug abuse effects. Amphetamine, cocaine, and similar stimulatory drugs increase levels of dopamine in the brain and can cause symptoms that resemble those present in psychosis. Hallucinogens may enhance dopaminergic transmission via 5-HT_{2A} receptor blockade (Curran et al., 2004; Lieberman et al., 1987; López-Giménez and González-Maeso, 2018). (2) Effects of antipsychotics. Almost all antipsychotics that are effective in the treatment of schizophrenia symptoms have been found to antagonize dopamine receptor binding, particularly at D_2 dopamine receptors (Grinchii and Dremencov, 2020; Seeman, 1987). (3) Altered dopamine synthesis. People with schizophrenia or at risk of developing schizophrenia have an increased capacity for dopamine synthesis in the striatum and an increased release of dopamine in response to stress. There is evidence that dopamine alteration may start before the onset of the disease (Howes et al., 2017; Howes and Murray, 2014). The implications of dopamine dysregulation for brain development are significant (Simpson and Kellendonk, 2017). It is speculated that the dopamine hypothesis is also supported by self-medication with nicotine, which may modulate the release of many neurotransmitters, including dopamine (de Leon and Diaz, 2005; Leonard et al., 2007). Additionally, smoking appears to be responsible for reducing the activity of monoamine oxidase, which catalyzes the oxidation of dopamine and other monoamine neurotransmitters to form ROS (Simpson et al., 1999). However, it is also possible that smoking is a risk factor for schizophrenia (Gurillo et al., 2015).

Among the main shortcomings of the dopamine hypothesis of schizophrenia is the fact that (i) dopamine levels in the brain change within minutes of antipsychotic administration, but symptoms do not improve until several days later, (ii) a significant portion of individuals with schizophrenia do not respond to non-clozapine antipsychotics, and (iii) phencyclidine and ketamine cause schizophrenia-like psychosis but are blockers of glutamate NMDA receptors (Javitt and Zukin, 1991; Lahti et al., 2001; Moncrieff, 2009).

6.2. Glutamate hypothesis

The dopamine hypothesis has so far been the main neurochemical hypothesis of schizophrenia. However, dopaminergic dysfunction cannot fully account for all symptoms of schizophrenia and disruption of the dopamine system may be induced by other upstream neurochemical changes. Based on the confirmed role of NMDA receptor activity in synaptic plasticity, cortical maturation, learning, and memory, a glutamate hypothesis based on NMDA receptor hypofunction has been proposed (Harrison and Weinberger, 2005). The **glutamate hypothesis** of schizophrenia suggests that function of NMDA receptor is impaired in this disease. Glutamate hypofunction in corticostriatal projections leads to triggering effects in the thalamocortical loop, which result in sensory overload, changes in dopamine levels, and psychotic symptoms.

The current glutamate hypothesis of schizophrenia proposes that the disease is caused by neurodevelopmental abnormalities of glutamate synapses, especially in the GABA interneurons in the cerebral cortex. Dysregulation of glutamatergic neurotransmission (mainly decreased NMDA receptor function) in the pathophysiology of schizophrenia is supported by new genetic and pharmacological findings, as well as postmortem studies and neuroimaging (Uno and Coyle, 2019).

NMDA receptor dysfunction may contribute directly to negative symptoms and cognitive dysfunction or indirectly to positive symptoms through the regulation of dopamine systems. Lower levels of $GABA_A$

receptors in the hippocampus have been observed in antipsychotic-free patients with schizophrenia (Marques et al., 2021), supporting the hypothesis that decreased GABA signaling in frontotemporal areas of the brain is involved in the pathogenesis of schizophrenia (Coyle, 2004). The **NMDA hypothesis** assumes hypofunction of NMDA receptors on GABA interneurons in the cerebral cortex and subsequent excessive glutamate signaling to the ventral tegmental area (VTA), which may lead to excessive dopamine signaling in the ventral striatum via the mesolimbic pathway (Stahl, 2018). This disinhibition model suggests that hypofunction of NMDA receptors on GABA interneurons in the cortex decreases the inhibition of glutamatergic pyramidal neurons, leading to excessive glutamate release. That is, while NMDA receptors may be hypofunctional in schizophrenia, glutamate release and signaling through other glutamate receptors may be excessive (Egerton et al., 2020).

The **excitotoxic hypothesis** of schizophrenia predicts that disinhibition of glutamate activity resulting from inhibition of NMDA receptors, and subsequent insufficient stimulation of GABA interneurons, lead to excitotoxic neuronal death in the cortical and hippocampal regions, leading to disease symptoms (Deutsch et al., 2001). It is thought that neuroinflammation associated with increased glutamate excitotoxicity during the acute phase of schizophrenia may lead to a reduction in glutamate and glutathione in the anterior cingulate cortex and to corresponding symptoms in some patients (Kumar et al., 2020; Palaniyappan et al., 2021b).

The **NMDA receptor hypofunction hypothesis** of schizophrenia (Snyder and Gao, 2020) specifies that risk factors cause epigenetic changes leading to decreased function of the glutamate NMDA receptor, which in turn causes impaired intracellular calcium homeostasis, neuronal activity, and synaptic plasticity. The result is dysfunction of dopaminergic and GABAergic neurotransmission leading to symptoms of schizophrenia. To date, the effects of drugs targeted to augment NMDA receptor function have been small to moderate in negative symptoms and small or nonsignificant in cognitive dysfunction in schizophrenia (Wu et al., 2021), indicating that a unification of the dopamine and glutamate approaches is warranted from a neurodevelopmental perspective.

The basis for the NMDA hypothesis includes the following observations: (1) schizophrenia-like symptoms may be induced in healthy subjects by NMDA receptor antagonists, such as phencyclidine, dizocilpine, and ketamine, (2) most genes that are associated with an increased risk of schizophrenia may affect the function of NMDA receptors or related signal transduction pathways, (3) mice with decreased NMDA receptor expression exhibit schizophrenia-like behavior, (4) dysregulated NMDA receptor subunits are usually seen in post-mortem tissue from subjects with schizophrenia, (5) elevated levels of glutamate and glycine in the brain in patients with the first episode of the disease imply NMDA receptor dysfunction, and (6) glutamate neurons may interact with GABA interneurons and dopamine neurons involved in the pathophysiology of schizophrenia (Javitt, 2010; Kim et al., 2018; Snyder and Gao, 2013).

In summary, according to the glutamate hypothesis, dopaminergic dysfunction is secondary to glutamatergic dysfunction. The interaction between the glutamate and dopamine systems in schizophrenia is that hypofunction of the glutamate NMDA receptor on GABA interneurons leads to disinhibition of glutamatergic projections on the dopamine system in the midbrain, increased glutamate release and ultimately increased activation of dopaminergic neurons (Howes et al., 2015). The convergence of GABA impairment and glutamate neurotransmission in the dorsolateral prefrontal cortex could explain the impairment of certain cognitive functions in schizophrenia (Lewis and Moghaddam, 2006).

6.3. Other hypotheses

According to the **serotonin hypothesis**, the risk factors (chronic stress, drugs) cause hyperfunction of the serotonergic system (excessive activation of 5-HT_{2A} receptors) in the cerebral cortex, especially on glutamate neurons in the anterior cingulate cortex and dorsolateral frontal lobe (Eggers, 2013). This leads to the release of glutamate in the VTA, increased activation of the dopamine mesolimbic pathway, and accumulation of dopamine in the ventral striatum and causes hallucinations and delusions (Stahl, 2018). Serotonin hypothesis is supported by changes in the serotonergic system observed in schizophrenia by (i) nuclear magnetic resonance spectroscopy (increased activation of phospholipase A_2 linked to 5-HT_{2A} receptors together with decreased activation of phospholipase C associated with glutamate signaling), (ii) positron emission tomography imaging with serotonergic ligands, and (iii) clinical effects of 5-HT_{2A} receptor blocking antipsychotics. Increased phospholipase A_2 activity in the prefrontal cortex may contribute to hypofrontality (Gattaz and Brunner, 1996), and the phospholipase A_2/cyclooxygenase pathway links changes in the serotonergic system and lipid metabolism to inflammatory processes in schizophrenia (Yang et al., 2021).

According to the **adenosine hypothesis** (Boison et al., 2012; Lara and Souza, 2000), a dysfunction of the purinergic system resulting in an imbalance in adenosine functions may be involved in the development of hypoglutamatergic and hyperdopaminergic conditions in schizophrenia. The novel adenosine hypothesis (Rial et al., 2014) suggests that there is a decrease in A_1 adenosine receptor function due to decreased A_1 receptor density and increased adenosine kinase activity; this is accompanied by decreased astrocytic A_{2A} receptor density and upregulation of neuronal A_{2A} receptor. The A_1 receptor and A_{2A} receptor imbalance disrupt the adequate encoding of information in neuronal circuits, leading to the development of schizophrenia endophenotypes.

It is supposed that the symptoms of schizophrenia may emerge, at least in part, through activation of cannabinoid CB_1 receptors, which are numerous in the brain. These are inhibitory receptors that are often localized presynaptically at GABA axon terminals and thus can affect the release of several neurotransmitters and modulate, for example, dopamine, serotonin, glutamate, acetylcholine, and opioid neurotransmission in various neuronal circuits (Bloomfield et al., 2016a; Cohen et al., 2019; Fantegrossi et al., 2018). Also, upregulation of the CB_2 receptor may inhibit presynaptic glutamate release in certain areas of the brain. Cannabinoid receptors are new drug targets for the treatment of neuroimmune and neurooxidative disorders such as schizophrenia (Dos Santos et al., 2021; Morris et al., 2021a). According to the **cannabinoid hypothesis** (El Khoury et al., 2012; Emrich et al., 1997; Garani et al., 2021; Müller-Vahl and Emrich, 2008), schizophrenia is associated with changes in the endocannabinoid system, especially with increased activation of CB_1 receptors located on GABA interneurons in the VTA, basolateral amygdala, and medial prefrontal cortex. It leads to hyperdopaminergic and hypoglutamatergic conditions in certain areas of the brain and to the disease symptoms. Dysfunction of the endocannabinoid system in schizophrenia is thought to be caused by neuroinflammation and nitrosative and oxidative stress (Morris et al., 2022a; Morris et al., 2022b). The hypothesis was supported by the finding that cannabis use in adolescence is a significant independent risk factor for schizophrenia (Belbasis et al., 2018). Cannabis use is thought to alter the normal development of cerebral dopamine systems, shift the physiology of neurotransmitters toward schizophrenia, and reduce blood flow to the frontal and temporal lobes (Cohen et al., 2008).

7. Integrative approach to schizophrenia hypotheses

Based on neuropathological studies of schizophrenia, new mixed hypotheses have been presented, integrating neurodevelopmental and neurodegenerative models and involving the interconnection of neurochemical, immune, and inflammatory changes in the brain (Altamura et al., 2013). This means that various neuroinflammatory/immune and neurotransmitter systems are being investigated to understand the mechanisms of the symptoms of schizophrenia. Neuroinflammation, oxidative and nitrosative stress, mitochondrial dysfunction, and

neurodegeneration in conjunction with impaired brain development are processes that may trigger pathological changes in neurotransmitter systems leading to symptoms of schizophrenia. The integrative approach can also include the hypothesis about the relationship of the gut microbiome to schizophrenia and the hypothesis explaining gender differences.

7.1. Neuroinflammation

In the **immune model** (the macrophage-T lymphocyte theory) of schizophrenia, chronically activated macrophages and T lymphocytes, along with excessive IL2 and other cytokine secretions, were proposed as the biological mechanism of schizophrenia. The hypothesis assumes that long-term excessive release of certain cytokines can lead to disorders of neurotransmission and neurodevelopment (Smith, 1992; Smith and Maes, 1995). Neuroprogressive changes in schizophrenia are due to several mechanisms, including disorders in neurotransmitter-mediated signal transduction, oxidative and nitrosative stress, immune-inflammation, tryptophan catabolite pathway, and mitochondrial dysfunction (Anderson and Maes, 2013).

The pathophysiology of schizophrenia includes also elevated microglial activity (Bloomfield et al., 2016b). The **microglial hypothesis** of schizophrenia suggests that immune-inflammatory factors (such as interferon-γ and lipopolysaccharide), which can be triggered by various stress events, activate microglia in the brain. Activated microglia release free radicals and pro-inflammatory cytokines, which cause neurodegeneration, white matter abnormalities, and reduced neurogenesis. Such neuron-microglia interactions may play a significant role in the pathophysiology of schizophrenia (Monji et al., 2009).

According to the **microglial two-hit model** of schizophrenia (Howes and McCutcheon, 2017), perinatal activation of microglia leads to their primed state, and subsequent stress in adolescence can trigger pathological overactivation of microglia, leading to cortical loss and disease symptoms. This model assumes that microglia play a significant role in pruning cortical synapses and that loss of cortical synapses and cortical volume in schizophrenia may be due to developmental changes in microglia (caused by genetic factors, perinatal insults, and early-life stress). Microglia show a hyperactive response to later stress and shift to the proinflammatory M1 phenotype. Microglial overactivation induced in early adulthood by stress or immune activation can lead to excessive pruning of synapses in areas of the brain sensitive to stress, such as the prefrontal cortex and hippocampus. This could explain the structural changes in the brain in schizophrenia and the development of negative and cognitive symptoms.

Based on post-mortem analyses, genetic association studies, transcriptomic studies, and studies of astrocytes in animal models, the hypothesis of **altered astrocyte activity** in schizophrenia was proposed that early astrocyte dysfunction may trigger the pathogenesis of schizophrenia. The hypothesis is based on findings that astrocytes influence neurodevelopmental processes related to the pathogenesis of schizophrenia, including glutamate, synaptogenesis, synaptic pruning, and myelination (de Oliveira Figueiredo et al., 2022; Notter, 2021).

According to the **integrated model of glial cells** in schizophrenia (Dietz et al., 2020), microglial activation during embryogenesis leads to delayed differentiation of oligodendrocytes and astrocytes, resulting in cortical and subcortical abnormalities in white matter integrity. Impaired astrocyte differentiation leads to glutamatergic dysfunction, disruption of potassium homeostasis, and dysregulation of growth factors and neuromodulators. Glial cell dysfunction results in brain dysconnectivity and dysregulated synaptic transmission, causing symptoms of schizophrenia.

Neurotransmitters, including dopamine, acetylcholine, serotonin, and glutamate, may also regulate immune cells and immunity (Franco et al., 2007). Based on the observation of a common association of schizophrenia with both stress and chronic neuroinflammation in the brain (Anderson and Maes, 2013), the vulnerability-stress model has been extended to the **vulnerability-stress-inflammation model** (Müller, 2018), according to which schizophrenia symptoms are associated with specific changes in dopaminergic, serotonergic, noradrenergic, and glutamatergic neurotransmission caused by stress, neuroinflammation, and microglial activation. According to this model, genetic vulnerability and cellular stress associated with infectious disease during pregnancy can induce a proinflammatory immune status and developmental changes in the brain that lead to obstetric complications or disrupt the further development of the glutamate system. Reexposure to stress at a later age may be followed by excessive cytokine release, astrocyte activation or loss, dopaminergic hyperactivity, and glutamate NMDA receptor dysfunction, leading to symptoms of schizophrenia.

In line with the vulnerability-stress-inflammation model of psychiatric disorders is the **mild encephalitis hypothesis** (Bechter, 2013; Bechter et al., 2014), according to which the onset or course of the disease in a subset of patients is associated with a low-level inflammatory process in the brain in the form of mild chronic encephalitis (Bechter, 2020). The hypothesis is supported by several psychoneuroimmunological findings and altered blood-brain-barrier permeability in schizophrenia (Najjar et al., 2017). According to the mild encephalitis hypothesis, schizophrenia could be considered a chronic but treatable neurological disease (Riedmuller and Muller, 2017).

A novel concept has been developed based on the immune-inflammatory response system (IRS) and the compensatory immune-regulatory reflex system (CIRS) interaction (Maes and Carvalho, 2018). The **immune-inflammatory response system and compensatory immune-regulatory reflex system theory** of schizophrenia (Roomruangwong et al., 2020) suggests that the acute episode of the disease is accompanied by induction of IRS activation (via induction of macrophagic M1 and T helper-1 phenotypes and subsequent immune processes), whereas the IRS response may be potentiated by deficits in CIRS. Increased levels of IRS cytokines and CIRS products may exert neurotoxic effects and cause the symptoms of schizophrenia. Changes in the functions of both systems and an adequately developed CIRS response may weaken IRS activation and promote spontaneous remission. Such a sensitized immune response may contribute to the formation of a new homeostatic setpoint after fading of the acute episode, which may indicate an increased susceptibility to further episodes of the disease.

The causal links between impaired synaptic connectivity in schizophrenia and the effects of specific immune factors are not well known (McAllister, 2014); feedback between inflammation and oxidative stress undoubtedly plays a key role (Bitanihirwe and Woo, 2011). Although some specific changes in neuromodulatory circuits and brain function associated with immune system activation have been revealed (Comer et al., 2020), these are mostly changes also observed in other neuropsychiatric diseases. There is a need to identify more specific markers for neuroinflammation in schizophrenia. In this area, it can be helpful to clarify how the immune system regulates brain circuits and vice versa, e.g., through exosomes (Harrell et al., 2021).

7.2. Oxidative and nitrosative stress

The **oxidative stress hypothesis** has become an attractive hypothesis to explain the pathophysiology of schizophrenia based on changes caused by free radicals and dysregulation of the antioxidant defense system (Bitanihirwe and Woo, 2011; Cadet and Kahler, 1994; Murray et al., 2021; Reddy and Yao, 1996; Wu et al., 2013). Oxidative and nitrosative damage to nucleic acids, proteins, and lipids impairs the viability, survival, and function of neurons and glial cells, which induces or accompanies processes associated with the onset and progression of schizophrenia, such as impaired neurodevelopment, neurotransmission, and intracellular and intercellular signaling, immune dysfunction, and neuroinflammation. Thus, oxidative stress is implicated in many biological hypotheses of schizophrenia, including neurodevelopmental,

dopamine, glutamate, immune, and dysconnectivity hypothesis (Bitanihirwe and Woo, 2011; Lin and Lane, 2019; Murray et al., 2021; Vallee, 2022).

The **hypothesis of altered inhibitory neurotransmission** propose that genetic and environmental factors lead to elevated oxidative stress in brain cells followed by oxidative damage of cortical parvalbumin interneurons, excitation-inhibition imbalance, and cognitive deficits in schizophrenia (Sullivan and O'Donnell, 2012). Dysfunctional GABAergic inhibition in schizophrenia is supported by the observation of reduced expression of reelin and glutamic acid decarboxylase 1 (GAD1) in postmortem brains of schizophrenia patients (Guidotti et al., 2000).

Neuronal connectivity and prefrontal cortex detachment in schizophrenia are associated with abnormalities in neuronal myelination (Davis et al., 2003). Myelination is affected by the function of mature oligodendrocytes, with oligodendrocyte precursor cells being extremely sensitive to oxidative stress (Uranova et al., 2011). Because oligodendrocytes express excitatory glutamate receptors, deficiency of glutamatergic neurotransmission in schizophrenia may reflect oligodendroglial changes (Martins-de-Souza, 2010). According to the **redox-induced prefrontal oligodendrocyte precursor cell-dysfunctioning hypothesis** of schizophrenia (Maas et al., 2017), the combination/interaction of environmental, genetic, and epigenetic factors causes the accumulation of ROS in oligodendrocyte precursor cells. During late adolescence, elevated levels of ROS disrupt the signal transduction processes in these cells. Dysfunction of oligodendrocyte precursor cells is associated with a relatively late onset of prefrontal cortical myelination. Thus, ROS-induced hypomyelination and disruption of connectivity in the prefrontal cortex may occur leading to the onset of schizophrenia.

The **glutathione-deficiency hypothesis** of schizophrenia suggests that early glutathione deficiency may contribute to the dysfunction of prefrontal parvalbumin interneurons and to excitotoxic damage to pyramidal cells, reduced density of dendritic spines, reduced stability of axonal projections, and disruption of myelin formation (Palaniyappan et al., 2021a).

Oxidative and nitrosative stress can also affect the function of cannabinoid receptors and thereby deregulate redox pathways mediated by the endocannabinoid system (Morris et al., 2022b). The source of ROS can be monoamine oxidase-catalyzed oxidation of monoamine neurotransmitters, which produces hydrogen peroxide. Hydrogen peroxide can oxidize ferrous ions (Fe^{2+}) to form the hydroxyl radical (Fenton reaction), which is a very reactive free radical. Abnormal neurotransmitter metabolism and iron deficiency can induce oxidative stress and contribute to schizophrenia (Insel et al., 2008).

Oxidative and nitrosative stress and impaired antioxidant defense may be a common final mechanism in development of schizophrenia (Boskovic et al., 2011; Flatow et al., 2013; Fraguas et al., 2019). Oxidative stress, which is closely associated with a few pathophysiological processes, such as inflammation, oligodendrocyte abnormalities, mitochondrial dysfunction, NMDA receptor hypoactivity, and GABA interneuron damage, has become an essential part of explaining the pathophysiology of schizophrenia (Bitanihirwe and Woo, 2011; Murray et al., 2021). Oxidative stress biomarkers might vary with disease development. E.g., total antioxidant status, red blood cell catalase, or plasma nitrite appear as state markers, while red blood cell superoxide dismutase appears as a trait marker for schizophrenia (Flatow et al., 2013).

Oxidative stress is increased in schizophrenia (Guler et al., 2021). It contributes to the pathophysiology of schizophrenia mainly by causing membrane dysfunction, such as increased membrane permeability and decreased fluidity leading to disturbances in intracellular signaling, receptor dysfunction, and increased neurotoxicity (Morris et al., 2016). In addition, the thioredoxin system, the glutathione system, and the nuclear factor erythroid 2-related factor 2 (Nrf2) system are disrupted in schizophrenia, both in the brain and in the periphery (Morris et al., 2021b). Altered glutathione redox state (Palaniyappan et al., 2021a; Yao et al., 2006) and increased oxidative damage in schizophrenia (Cecerska-Heryc et al., 2022; Wu et al., 2013) indicate that, although oxidative stress may not be the primary cause of the disease, it may be a regulator of the course of schizophrenia.

Mitochondria are a significant source of intracellular ROS and NO; therefore, oxidative and nitrosative stress may be a downstream effect of mitochondrial dysfunction (Morris et al., 2020). During the inflammatory response, pro-inflammatory T cells are activated, and free radicals are produced that are potentially toxic to neurons and glia. There is an interplay between neuroinflammation and oxidative stress that is modulated by the WNT/β-catenin pathway, inflammatory factories, and oxidative stress factors (Vallee, 2022).

7.3. Mitochondrial dysfunction

The **mitochondrial hypothesis** of schizophrenia suggests a key role for mitochondrial dysfunction in the development of impaired neuronal plasticity and activity, causing imbalances in certain brain circuits and ultimately abnormal behavior (Ben-Shachar, 2020). Mitochondrial dysfunction may be included in several previously mentioned hypotheses of schizophrenia, including the oligodendrocyte hypothesis, where mitophagy may be thought to be elevated in oligodendrocytes, contributing to schizophrenia-related white matter neuropathology (Bernstein et al., 2020). *In vitro* measurement data suggest that the mitochondrial effects of current antipsychotics are likely related to adverse effects and are due to drug-induced decreased ATP production and increased ROS production (Cikánková et al., 2019; Ľupták et al., 2021a); however, due to mitochondrial dysfunctions observed in neurodegenerative diseases, bipolar disorder, and schizophrenia, new psychotropic drugs focus on selected mitochondrial targets (Bar-Yosef et al., 2020; Ben-Shachar, 2017; Fišar et al., 2021).

Post-mortem studies provide evidence of regional reductions in neuronal and glial density, leading to the **apoptotic hypothesis** of schizophrenia and suggesting that apoptosis may be involved in the development of schizophrenia (Jarskog et al., 2005). Apoptotic activity at the first onset of schizophrenia is thought to contribute to reduced neuronal survival and disruption of synaptic plasticity (Glantz et al., 2006). In response to intracellular signals generated by cellular stress and mitochondrial dysfunction, the intrinsic apoptosis pathway can be triggered by the release of proapoptotic factors from mitochondria. Moreover, the endoplasmic reticulum stress and death-receptor pathways interact with the mitochondrial apoptotic pathway. The data in schizophrenia show dysregulation of apoptosis in cortical areas of the brain, and non-lethal localized apoptosis may occur in the early stages of the disease (Jarskog, 2006).

Decreased cardiolipin metabolism in the human prefrontal cortex in schizophrenia (Yu et al., 2020) links the membrane and mitochondrial hypothesis of schizophrenia. The oligodendrocyte hypothesis is linked to the glutamate and mitochondrial hypotheses via glutamate metabolism in the brain. In astrocytes and oligodendrocytes, glutamate interacts with ammonia to form glutamine (the necessary enzymes are not expressed in neurons), glutamine is transported to neurons and there is converted in mitochondria to glutamate. This glutamine cycle prevents the loss of α-ketoglutarate from the Krebs cycle in neurons upon excessive release of glutamate from nerve endings; disruption of the glutamine cycle means mitochondrial dysfunction and oxidative stress and vice versa.

Disruption of brain cell functions, neuroplasticity, and brain circuits in schizophrenia can be caused by impaired energy metabolism (Duarte and Xin, 2019; Maurer et al., 2001; Zuccoli et al., 2017) and increased oxidative stress, which are processes regulated primarily by mitochondria. Evidence suggests that mitochondrial dysfunctions and oxidative stress participate in the pathophysiology of schizophrenia (Morris et al., 2020; van Rensburg et al., 2022; Wood et al., 2009). Indeed, *in vivo,* and post-mortem brain imaging studies have shown an impairment of energy metabolism in the brains of people with schizophrenia. The most used

biomarkers that can be measured in peripheral tissue include antioxidant enzymes, lipid peroxidation markers, oxidatively damaged proteins and DNA (Bošković et al., 2011). Mitochondrial dysfunction can manifest itself in impaired neuroplasticity, e.g., in neurons with defective synaptic activity, or in oligodendrocytes in myelin pathology leading to disconnection of the cerebral circuits. Post-mortem studies show that mitochondria are affected in schizophrenia differently in different areas of the brain and in different cell types (Roberts, 2021), which supports the view that mitochondrial dysfunction may be responsible for various symptoms of the disease.

7.4. Neurodegeneration

Some changes in brain function in schizophrenia can be better explained by neurodegenerative rather than neurodevelopmental changes. The **neurodegenerative model** (Stone et al., 2022) assumes that brain degeneration participates in the development of schizophrenia in some people with a chronic course of the disease. The model explains age-related dysfunctions in chronic schizophrenia, such as progressive impairment of cognitive functions and white and gray matter integrity (accelerated aging), as a reflection of neurodegenerative processes. The absence of gliosis is a prominent argument against neurodegeneration in schizophrenia. Aging trend of BDNF concentration in the prefrontal cortex supported an abnormal brain aging process in some patients with schizophrenia (Rao et al., 2015), but does not indicate progressive neurodegeneration. However, clinical and neuroimaging evidence of degeneration has been found in certain subgroups of patients with schizophrenia (Aberizk et al., 2022; Gupta and Kulhara, 2010). Excitotoxic hypothesis proposes that neurons degenerate because of excessive glutamatergic neurotransmission (Deutsch et al., 2001). Combined neurodevelopmental and neurodegenerative hypothesis suggest that schizophrenia may be a neurodegenerative process superimposed on a neurodevelopmental abnormality (Kochunov and Hong, 2014).

7.5. Gut microbiome

Recently, there has been growing interest in the relationship between the **gut microbiome** and schizophrenia. Dysbiosis (microbiome profiles that differ significantly from controls and that could have functional significance in pathological processes) could fit into the known hypotheses of the pathogenesis of schizophrenia with a focus on neurodevelopment, neuroinflammation, tryptophan metabolites, BDNF activity, and hypothalamic–pituitary–adrenal (HPA) axis dysregulation (Misiak et al., 2020; Szeligowski et al., 2020; Wiedlocha et al., 2021). It is thought that the microbiome may affect brain development through epigenetic mechanisms (Alam et al., 2017). Signaling pathways from the gut microbiome to the brain include (i) direct activation of the vagus nerve; (ii) production of various metabolites that can cross the blood–-brain barrier and regulate brain functions; and (iii) an immune system whose cytokines affect neurophysiology (Sampson and Mazmanian, 2015; Zeng et al., 2021). Research suggests that microbiome disruption may be involved in the etiology of neurodevelopmental disorders (Forssberg, 2019). However, current data showing microbiome changes in schizophrenia are still insufficient to confirm the hypothesis of an association between microbiome changes and an increased risk of schizophrenia (Szeligowski et al., 2020). In addition, the hypothesis that the gut microbiome is a new potential target for intervention in schizophrenia (antibiotics, antimicrobials, prebiotics, probiotics, and fecal transplant) has not been validated (Minichino et al., 2021). Further research and more clinical studies are needed to verify the gut microbiome hypothesis, including monitoring of sex differences in the regulation of the gut-microbiota-brain axis in schizophrenia (Manosso et al., 2021).

7.6. Gender differences

Genetic, environmental, neurodevelopmental, neuroendocrine, and neurochemical approaches are integrated into schizophrenia hypotheses explaining gender differences. Gender/sex-dependent associations between susceptibility to schizophrenia and various biological influences have been studied for a long time (Goldstein et al., 2013). A meta-analysis assessing the differences in the incidence of schizophrenia by gender confirmed that schizophrenia is modestly more common in men than in women with an incidence rate ratio of 1.70 (Jongsma et al., 2019). Polygenic risk for schizophrenia on cognitive functioning in healthy individuals is sex-specific (Koch et al., 2021). Clinical and epidemiological studies of schizophrenia evidenced that age of onset, symptoms, and response to antipsychotic treatment differ between men and women, reflecting certain differences in neurodevelopment and cognition (Abel et al., 2010; Ceskova et al., 2015; Leung and Chue, 2000; Li et al., 2016; Seeman, 1997, 2021; Tamminga, 1997). This, together with the observation that males with an extra-X chromosome (Klinefelter's syndrome) may have an increased prevalence of schizophrenia (DeLisi et al., 2005) has led to the formulation of **sex chromosome (XY gene) hypothesis**. According to this hypothesis, pathological changes causing psychotic illness are associated with changes on the X and Y chromosomes and are epigenetic in nature (Crow, 2013; DeLisi and Crow, 1989; Li et al., 2016). This hypothesis has not yet been denied or confirmed (Bache and DeLisi, 2018). The hypothesis is supported by the finding that sex chromosomes may play a role in neurodevelopment and contribute to sex-specific cognitive functions (Hong and Reiss, 2014). GWAS examining genetic influences on age at onset and disease severity did not reveal any significant sex-specific associations (Bergen et al., 2014). Recently, slight differences between male and female GWAS have been described (Guo et al., 2021). A large genome-wide genotype-by-sex analysis of psychotic disorders confirmed substantial genetic overlap between the sexes; at the same time, it found that significant gender-dependent processes include processes related to neuronal development and immune and vascular functions regulated at the level of variants, genes, and signaling pathways (Blokland et al., 2022).

A systematic review evaluating gender differences in the association of environmental exposures with psychosis (Pence et al., 2022) confirmed a stronger association of (i) childhood adversity with risk of psychotic illness or earlier age of psychosis in women, (ii) substance use with earlier age of onset disease in women, (iii) urbanicity or migration with a risk of developing schizophrenia in men. Changes in the levels of peripheral hormones may contribute to gender differences in the severity of symptoms and the course of schizophrenia. **Estrogen hypothesis** suggests that estrogens (particularly estradiol) are responsible for some of the gender differences observed in schizophrenia (such as in premorbid adjustment, onset age, treatment response, and illness course); their effect is based on the protection against the development of the disease and on the alleviation of the severity of negative symptoms (Grigoriadis and Seeman, 2002; Hafner, 2003; Li et al., 2016; Seeman, 1982, 1997). The estrogen hypothesis is supported by the observation of fluctuations in psychotic symptoms in schizophrenic women during their menstrual cycle, differential efficacy of antipsychotics, and decreased plasma estrogen levels in women and men with schizophrenia. Due to the effect of estrogens on neurodevelopment, synaptic plasticity, and neurotransmission (dopamine, glutamate, and GABA), estrogen-regulated schizophrenia susceptibility genes and signaling pathways affect the manifestation of schizophrenia rather than estrogens alone (Grigoriadis and Seeman, 2002; Li et al., 2016; Olsen et al., 2008; Williams et al., 2021). Evidence of the involvement of other gonadal hormones, such as progesterone and testosterone, in the pathophysiology of schizophrenia is weaker (Brzezinski-Sinai and Brzezinski, 2020).

Another hormonal hypothesis is the **oxytocin hypothesis** of schizophrenia (Rosenfeld et al., 2011). The hypothesis suggests that abnormal interactions between dopaminergic reward systems,

dysfunctional amygdala, and oxytocin lead to improper processing of environmental emotional stimuli, which may lead to negative symptoms of schizophrenia. The hypothesis is based on the observation that (i) peripheral oxytocin and arginine vasopressin modulate regional brain activity differently in male and female patients with schizophrenia (Rubin et al., 2018), and (ii) higher oxytocin levels may alleviate the severity of positive symptoms and overall psychopathology in women and improve prosocial behavior in both sexes (Rubin et al., 2011).

8. Conclusion

Schizophrenia has been concluded to be a multifactorial disorder with a strong genetic component in susceptibility to the disease; a combination of environmental risk factors with several risk genes with small effects is necessary for the development of the disease (Karayiorgou and Gogos, 1997, 2006; Trifu et al., 2020; Weinberger, 2019). Sensitivity to stress and epigenetic, neurodevelopmental, and neurochemical changes are interrelated, making it difficult to establish a clear sequence of processes leading to the onset and progression of schizophrenia. It is generally believed that genetic factors in combination with environmental influences and allostatic load lead to complex changes in the activity of the dopaminergic, glutamatergic, serotonergic, and GABAergic systems that are associated with the symptoms of schizophrenia (Snyder and Gao, 2020). Psychotic symptoms can arise through CNS dysfunction induced by risk factors either directly or indirectly through non-CNS dysfunction (Pillinger et al., 2019).

Molecular mechanisms leading to specific cellular, neuroanatomical, and behavioral hallmarks of schizophrenia due to impaired immune pathways, mitochondrial function, and ROS production are still not clear enough. Different risk factors and biomarkers can converge to the same symptoms of schizophrenia, showing that the primary cause of the disease can be highly individual. Prevention should be targeted at risk factors, treatment mainly at neurochemistry and neuroplasticity of the brain. The additive and feedback effects of various risk factors and biomarkers on certain signaling pathways leading to exceeding certain thresholds into a disease state appear to be responsible for a large number of biological hypotheses of schizophrenia. The biological hypotheses of schizophrenia can be summarized in **a neurodevelopmental-vulnerability-neurochemical model** that links the various causes of disease susceptibility to the common neurochemical and neuroplastic nature of schizophrenia symptoms. Schizophrenia is a neurodevelopmental disease whose symptoms are caused by impaired synaptic plasticity and impaired neurotransmission in certain neuronal circuits in the brain. Neurodevelopmental disorder can be caused by both genetic and epigenetic influences, as well as environmental influences (birth complications, stress, toxins, and drugs) and gene-gene or gene-environment interactions over time. Impaired neurodevelopment leads to an increased susceptibility to schizophrenia through an increased sensitivity or pathological response to stress and/or neuroinflammation. The onset of symptoms of schizophrenia is associated with impaired function of neuronal circuits and impaired neurotransmission, especially at the level of signal transduction through chemical synapses of monoamine, glutamate, cannabinoid, and GABA neurons. Impaired synaptic plasticity includes impaired cellular energy and transport and changes in the number and strength of synapses, i.e., changes in the activity of neurotrophic factors, neurotransmitters and their receptors and transporters, ion channels, effector enzymes and intracellular components of signaling pathways. The direct causes of impairment of neuronal functions and synaptic plasticity are reactive oxygen and nitrogen species and the effects of degrading enzymes in the apoptotic signaling pathway (i.e., processes associated with response to stress events, neuroinflammation, calcium imbalance, and mitochondrial dysfunction).

The neurodevelopmental-vulnerability-neurochemical model can be used for the spectrum of schizophrenia and other psychotic disorders. The generality of this model reflects the fact that schizophrenia is a complex disease associated with many internal and environmental factors and that there are several types of schizophrenia with symptoms caused by various neuroanatomical and neurochemical causes. The usefulness of the model lies in the specification of brain processes, on which it is appropriate to focus attention on the search for new biomarkers necessary for the formulation of advanced biological hypotheses of a certain type of schizophrenia with specific psychotic symptoms.

Declaration of Competing Interest

The author declares no conflict of interest.

Acknowledgment

This work was supported by Charles University, Prague, Czech Republic (project Cooperatio, research area Neurosciences).

Appendix A. Supplementary data

Supplementary material to this article can be found online at https://doi.org/10.1016/j.pnpbp.2022.110626.

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