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Schizophrenia: Current Advances in Neurobiology, Genomics, Diagnostic Strategies, and Novel Therapeutic Interventions

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ABSTRACT

Schizophrenia is a severe, chronic, and highly heterogeneous neuropsychiatric disorder that affects approximately 1% of the global population. It is one of the leading causes of disability among young adults and imposes a substantial clinical, social, and economic burden worldwide. The disorder is characterized by positive and negative symptoms, cognitive impairment, and social dysfunction, all of which markedly reduce patients' quality of life. Despite decades of intensive research, the underlying mechanisms of schizophrenia remain incompletely understood. Current evidence indicates that its pathogenesis arises from complex interactions among genetic susceptibility, neurodevelopmental abnormalities, environmental risk factors, immune dysregulation, and dysfunction of multiple neurotransmitter systems. Recent advances in molecular genetics, epigenetics, neuroimaging, and systems neuroscience have fundamentally reshaped our understanding of the disease. Schizophrenia is now recognized as a disorder of disrupted neural circuitry, impaired synaptic plasticity, and abnormal brain connectivity rather than a consequence of a single

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neurotransmitter imbalance. This review provides a comprehensive and up-to-date overview of schizophrenia, covering its epidemiology, clinical manifestations, major risk factors, molecular pathophysiology, diagnostic advances, and emerging therapeutic strategies. Particular emphasis is placed on the interactions among dopaminergic, glutamatergic, γ-aminobutyric acid (GABA)-ergic, serotonergic, cholinergic, and neuroinflammatory pathways and their contributions to cortical circuit dysfunction, cognitive decline, and psychotic symptoms. Finally, the review integrates current molecular, genetic, neurodevelopmental, and clinical evidence to highlight recent advances in schizophrenia research and their implications for precision diagnosis, personalized medicine, and the development of mechanism-based therapeutic interventions.

Key words: Neuropsychiatric, Cognitive Impairment, Epigenetics, Pathophysiology, Clinical Manifestations, Diagnostic Advances

Introduction

Historically, schizophrenia was first described by Emil Kraepelin in the late nineteenth century as dementia praecox. In the early twentieth century, Paul Eugen Bleuler introduced the term schizophrenia, derived from the Greek words skhizein (to split) and phren (mind), to describe the fragmentation of psychic functions that characterizes the disorder (1, 2). Schizophrenia is a severe, chronic, and heterogeneous psychiatric disorder that typically develops during late adolescence or early adulthood and is associated with substantial disability, reduced life expectancy, and considerable socioeconomic burden (3, 4). It affects approximately 24 million people worldwide, representing 0.7–1% of the global population (5). Clinically, schizophrenia is characterized by positive symptoms (hallucinations, delusions, and disorganized speech), negative symptoms (avolition, anhedonia, blunted affect, and alogia), and cognitive impairments involving attention, memory, executive function, and social cognition. Cognitive deficits occur in nearly 80% of patients and are major determinants of long-term functional outcomes (6–9) (Figure 1).

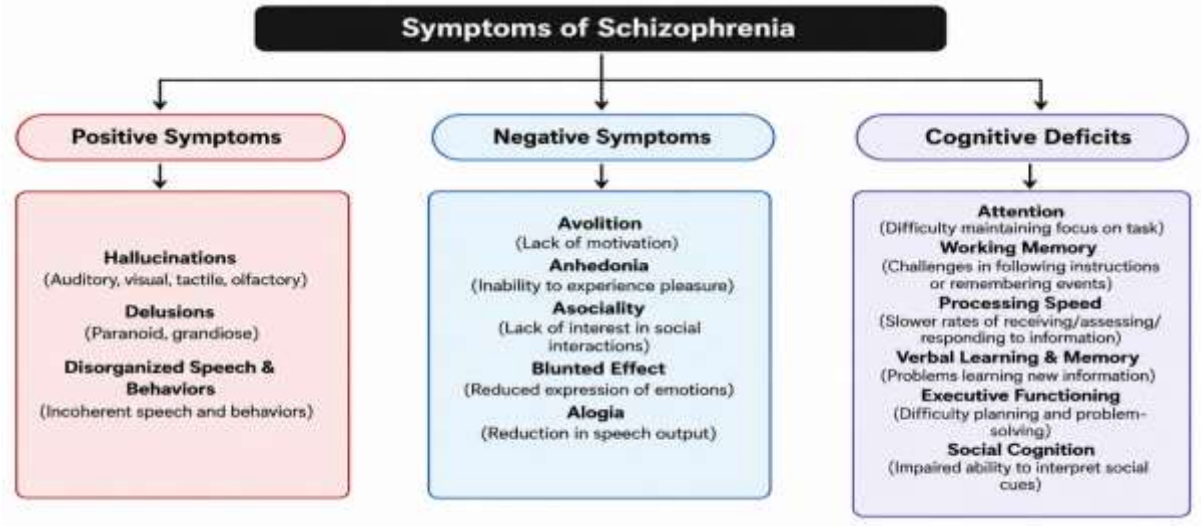


Figure 1. Positive, negative, and cognitive symptoms of schizophrenia.

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Schizophrenia is more common in males than females (1.4:1), with an earlier age of onset in men (18–25 years) than in women (25–35 years) (10). The disorder most frequently manifests between 14 and 30 years of age and represents a major contributor to the global burden of mental illness, particularly among young adults (11). In addition to its profound personal and social consequences, schizophrenia imposes substantial healthcare and economic costs worldwide (12). Although its precise etiology remains unknown, current evidence indicates that schizophrenia results from complex interactions among genetic susceptibility, environmental exposures, neurodevelopmental abnormalities, and adverse early-life experiences, including childhood trauma (13–15). Schizophrenia is increasingly recognized as a multifactorial neurodevelopmental disorder with heterogeneous etiopathological mechanisms (16–18). Recent advances in genome-wide association studies (GWAS), neuroimaging, and molecular neuroscience have identified numerous susceptibility genes, including DISC1, NRG1, DTNBP1, CACNA1C, GRIN2A, and DRD2, that regulate synaptic function, neuronal development, calcium signaling, glutamatergic neurotransmission, immune responses, and cortical maturation. Environmental factors, including prenatal infections, obstetric complications, childhood adversity, and abnormal synaptic pruning during critical stages of brain development, further contribute to disease susceptibility. In addition, immune dysregulation, neuroinflammation, and disturbances in dopaminergic and glutamatergic neurotransmission have emerged as central mechanisms underlying schizophrenia pathophysiology, providing new opportunities for improved diagnosis and targeted therapeutic interventions (19–23) (Table 1).

Table 1. Risk factors and proposed biological mechanism for schizophrenia

Risk factors category	Specific risk factors	Proposed biological mechanism
Genetic Factors	Family history of schizophrenia, polygenic risk variants, copy number variants (CNVs), DISC1, COMT, NRG1, CACNA1C, DTNBP1, C4 gene variants.	Inherited susceptibility leading to abnormal brain development, synaptic dysfunction, and altered neurotransmission.
Prenatal factors	Maternal infections (influenza, Toxoplasma gondii), maternal malnutrition, vitamin D deficiency, maternal stress, gestational diabetes.	Disrupted fetal Neurodevelopment through immune activation, inflammation, and impaired neuronal migration.
Perinatal factors	Birth hypoxia, preterm birth, low birth weight, obstetric complications.	Brain injury and impaired maturation of neural circuits during critical developmental periods.

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Neurodevelopmental factors	Abnormal neuronal migration, defective synaptic pruning, altered cortical maturation.	Formation of dysfunctional neural networks involved in cognition and perception.
Neurochemical factors	Dopamine hyperactivity, NMDA receptor hypofunction, GABAergic dysfunction, serotonergic imbalance.	Dysregulated neurotransmission causing psychotic, cognitive, and negative symptoms
Environmental factors	Urban upbringing, migration, childhood trauma, psychosocial stress, bullying, social isolation.	Chronic stress leading to dysregulation of the Hypothalamic–pituitary–adrenal (HPA) axis and altered brain development.
Epigenetic factors	DNA methylation, histone modification, microRNA dysregulation	Altered expression of genes involved in neurodevelopment and synaptic plasticity without changing DNA sequence.

According to the diagnostic and statistical manual of mental disorders, fifth edition, text revision (DSM-5-TR), the diagnosis of schizophrenia requires the presence of two or more characteristic symptoms—including delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms—accompanied by impaired social or occupational functioning (24, 25). Diagnosis is primarily based on clinical assessment using the DSM-5-TR and the International Classification of Diseases (ICD-11), the two most widely adopted diagnostic systems worldwide. While DSM-5-TR requires continuous signs of illness for at least 6 months, ICD-11 requires a minimum symptom duration of 1 month, facilitating earlier diagnosis and intervention (24, 26, 27). Current management of schizophrenia combines pharmacological treatment, psychosocial interventions, and supportive care. Antipsychotic medications remain the cornerstone of therapy. First-generation antipsychotics (FGAs), introduced in the 1950s and 1960s, and second-generation antipsychotics (SGAs), introduced in the 1990s, are both effective for controlling positive symptoms. However, SGAs generally demonstrate improved tolerability and fewer extrapyramidal adverse effects. Advances in neuroimaging have further improved understanding of the structural and functional brain abnormalities associated with schizophrenia (28–30).

Pathophysiology

Schizophrenia is a multifactorial neuropsychiatric disorder resulting from interactions among genetic susceptibility, environmental exposures, neurodevelopmental abnormalities, and neurotransmitter dysregulation (31, 32). The disorder has an estimated heritability of approximately 80%, with genome-wide association studies (GWAS) identifying susceptibility genes such as DISC1, NRG1, DTNBP1, CACNA1C, GRIN2A, and DRD2, which regulate synaptic function, neuronal development, calcium signaling, glutamatergic transmission, and immune responses.

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Environmental risk factors—including prenatal infections, obstetric complications, childhood trauma, cannabis use, urbanization, and migration—interact with genetic predisposition to increase disease susceptibility (33–42). In addition, abnormalities in dopaminergic, glutamatergic, and GABAergic neurotransmission, together with immune dysregulation and oxidative stress, are recognized as key contributors to schizophrenia pathophysiology (43–45).

The Dopamine hypothesis

The dopamine hypothesis remains one of the most influential models of schizophrenia, proposing that abnormal dopaminergic neurotransmission is central to the development of psychotic symptoms, particularly hallucinations, delusions, and thought disorder (3, 45). Dopamine dysfunction affects several major neural pathways (Figure 2).

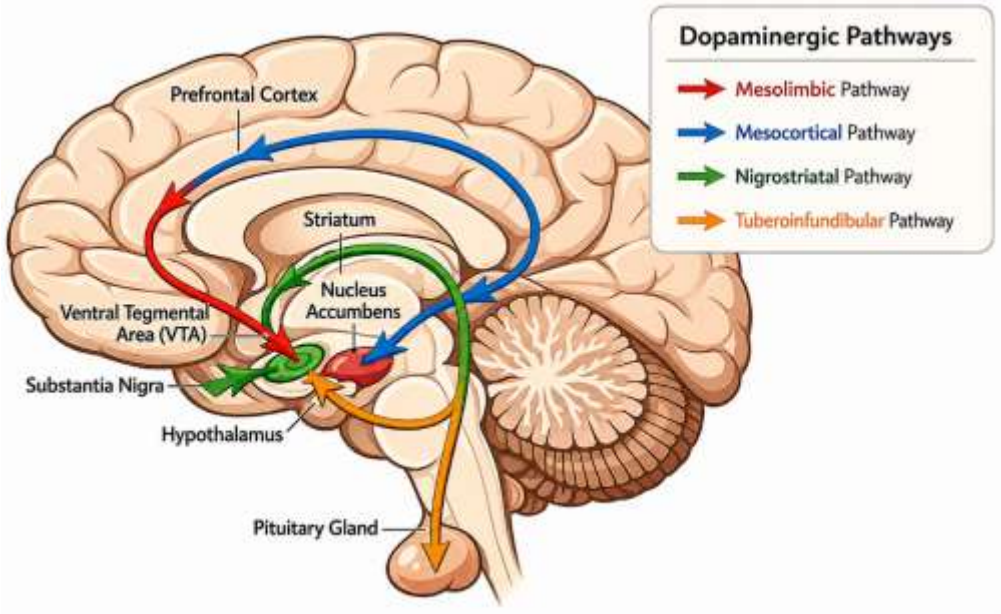


Figure 2. Dopamine pathways in the brain (3).

Mesolimbic pathway: Originating in the ventral tegmental area (VTA) and projecting to the nucleus accumbens and amygdala, this pathway regulates reward, motivation, and reinforcement. Hyperactivity of mesolimbic dopamine signaling causes excessive D2 receptor stimulation, producing the positive symptoms of schizophrenia (46–49).

Mesocortical pathway: This pathway projects from the VTA to the prefrontal cortex, including the dorsolateral and ventromedial prefrontal regions. Reduced dopaminergic activity within this circuit contributes to negative symptoms, including emotional blunting and reduced motivation, as well as cognitive deficits affecting attention, working memory, and executive function (49–51).

Nigrostriatal pathway: The nigrostriatal pathway extends from the substantianigra to the striatum and plays a critical role in motor control. Dopamine blockade within this pathway is primarily associated with extrapyramidal motor adverse effects during antipsychotic treatment.

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Tuberoinfundibular pathway: The tuberoinfundibular pathway connects the hypothalamus with the anterior pituitary, where dopamine suppresses prolactin secretion through D2 receptors. Antipsychotic-induced D2 receptor blockade disrupts this inhibition, resulting in hyperprolactinemia. Current evidence suggests that schizophrenia is characterized mainly by abnormal presynaptic dopamine synthesis and release rather than elevated basal dopamine concentrations (50, 53–55).

Glutamate hypothesis

Glutamate is the principal excitatory neurotransmitter in the central nervous system, accounting for approximately 80–90% of excitatory synaptic transmission and representing the most abundant amino acid neurotransmitter in the brain (57). Because excessive extracellular glutamate induces excitotoxic neuronal injury, its concentration is tightly regulated through the glutamate–glutamine cycle (Figure 3). Following synaptic release, glutamate activates postsynaptic receptors and is rapidly removed by excitatory amino acid transporters (EAATs) into astrocytes, where it is converted to glutamine by glutamine synthetase. Glutamine is subsequently transported back to presynaptic neurons, converted into glutamate by glutaminase, and repackaged into synaptic vesicles. This recycling process is closely coupled to cerebral energy metabolism and is essential for maintaining excitatory neurotransmission (56, 58, 59). Glutamate exerts its effects through ionotropic and metabotropic receptors. Ionotropic receptors include AMPA, NMDA, and kainate receptors, which mediate rapid excitatory neurotransmission and synaptic plasticity (56, 61). Metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors classified into three groups: Group I (mGluR1 and mGluR5), which are predominantly postsynaptic, and Groups II (mGluR2/3) and III (mGluR4, 6, 7, and 8), which are mainly presynaptic and regulate glutamate release (60). Among these receptors, NMDA receptors play a pivotal role in schizophrenia. Their activation requires glutamate binding, glycine or D-serine as co-agonists, and membrane depolarization to remove the magnesium block. NMDA receptor antagonists, including ketamine and phencyclidine (PCP), induce receptor hypofunction and reproduce schizophrenia-like symptoms, supporting the glutamate hypothesis of the disorder (62).

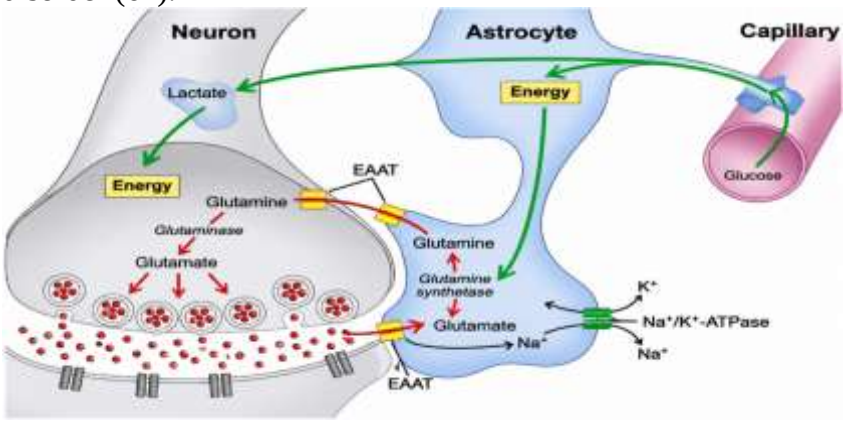


Figure 3. Glutamate/glutamine cycle. Glutamate removed from synaptic cleft by excitatory amino acid transporters (EAATs) into astrocytes and converted into

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glutamine by enzyme glutamine syntheses. Glutamine is then transported out of astrocytes into nerve terminals and converted back to glutamate via glutaminase (56).

The GABAergic hypothesis

The GABAergic hypothesis proposes that impaired γ-aminobutyric acid (GABA) neurotransmission contributes to schizophrenia. As the principal inhibitory neurotransmitter in the central nervous system, GABA maintains the balance between neuronal excitation and inhibition. Abnormal GABAergic signaling within the prefrontal cortex (PFC) has been associated with deficits in working memory, learning, and executive function observed in schizophrenia (63). Postmortem studies have demonstrated reduced expression of parvalbumin-positive interneurons, together with decreased levels of glutamate decarboxylase (GAD67) and GAD65, enzymes essential for GABA synthesis (64–66). These abnormalities impair inhibitory regulation of cortical pyramidal neurons, resulting in disrupted cortical network activity and cognitive dysfunction (Figure 4).

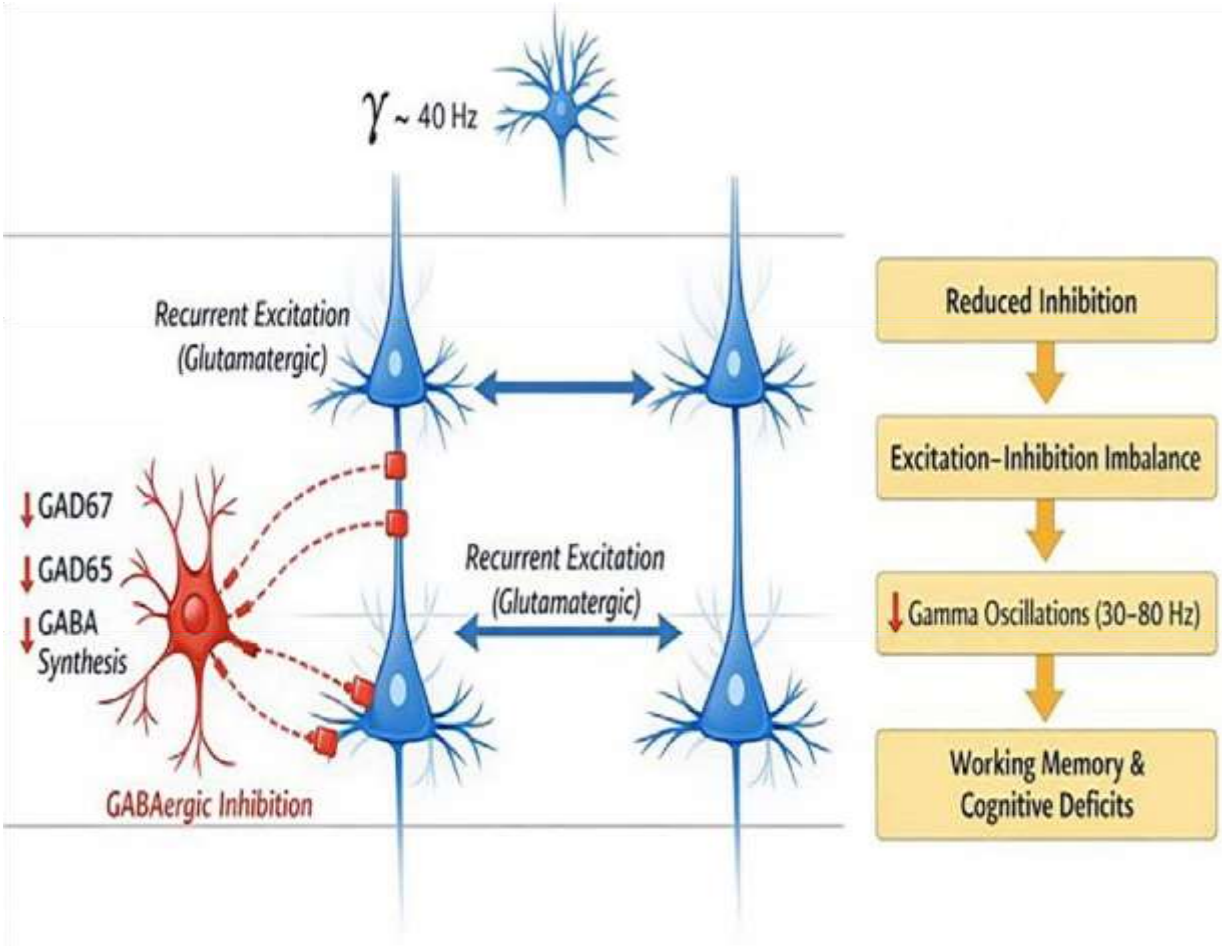


Figure 4. GABAergic interneuron dysfunction and excitation–inhibition imbalance in prefrontal cortical microcircuits implicated in schizophrenia

Experimental studies indicate that reduced GABA synthesis alone is insufficient to produce schizophrenia. Instead, abnormalities in synaptic structure, including loss of

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dendritic spines associated with reduced Arp2/3 expression in the prefrontal cortex, appear to interact with GABAergic dysfunction to promote schizophrenia-related behavioral and molecular changes (67, 68).

The Acetylcholine hypothesis

Individuals with schizophrenia exhibit a markedly higher prevalence of cigarette smoking than the general population, suggesting abnormalities in cholinergic neurotransmission involving both nicotinic and muscarinic receptors (70–79). Nicotine is thought to partially compensate for these deficits by improving cognitive performance and correcting abnormalities in eye-tracking and electroencephalographic (EEG) activity, supporting the self-medication hypothesis (80–82). Similarly, reduced positive symptoms have been reported in patients with schizophrenia who chew betel nut (83). Postmortem studies have identified reduced expression of muscarinic M1 and M4 receptors in the prefrontal cortex, hippocampus, and striatum, together with diminished upregulation of high-affinity nicotinic acetylcholine receptors (nAChRs) in smokers with schizophrenia. These findings indicate widespread cholinergic dysfunction and may explain the high prevalence of nicotine dependence in this population (82–86). Therapeutically, xanomeline, a selective M1/M4 muscarinic receptor agonist, particularly when combined with the peripheral anticholinergic trospium, significantly reduces Positive and Negative Syndrome Scale (PANSS) scores in patients with schizophrenia. Conversely, muscarinic antagonists can exacerbate psychotic symptoms, emphasizing the importance of cholinergic signaling in schizophrenia pathophysiology. Nevertheless, whether cholinergic dysfunction represents a primary disease mechanism or develops secondary to other neurobiological abnormalities remains uncertain (86–90).

Neurodevelopmental hypothesis

The neurodevelopmental hypothesis is one of the most widely accepted models explaining the pathogenesis of schizophrenia. It proposes that interactions between genetic susceptibility and prenatal or early postnatal environmental insults disrupt normal brain development, whereas clinical symptoms typically emerge during late adolescence or early adulthood (91–95). Critical developmental events, including neuronal migration, synaptogenesis, and cortical maturation during the second and third trimesters of pregnancy, are particularly vulnerable to these insults.

The widely accepted "two-hit" model suggests that an initial genetic or perinatal insult creates a vulnerable neural network, while a second insult during adolescence—when extensive synaptic pruning and myelination occur—precipitates the onset of schizophrenia (Figure 5). Excessive synaptic pruning, impaired synaptic plasticity, reduced oligodendrocyte function, and abnormal myelination may disrupt both local and long-range brain connectivity, particularly within the prefrontal cortex. Consequently, subtle cognitive deficits and minor motor abnormalities often precede the onset of psychosis, supporting schizophrenia as a disorder of abnormal neurodevelopment (96–105, 110).

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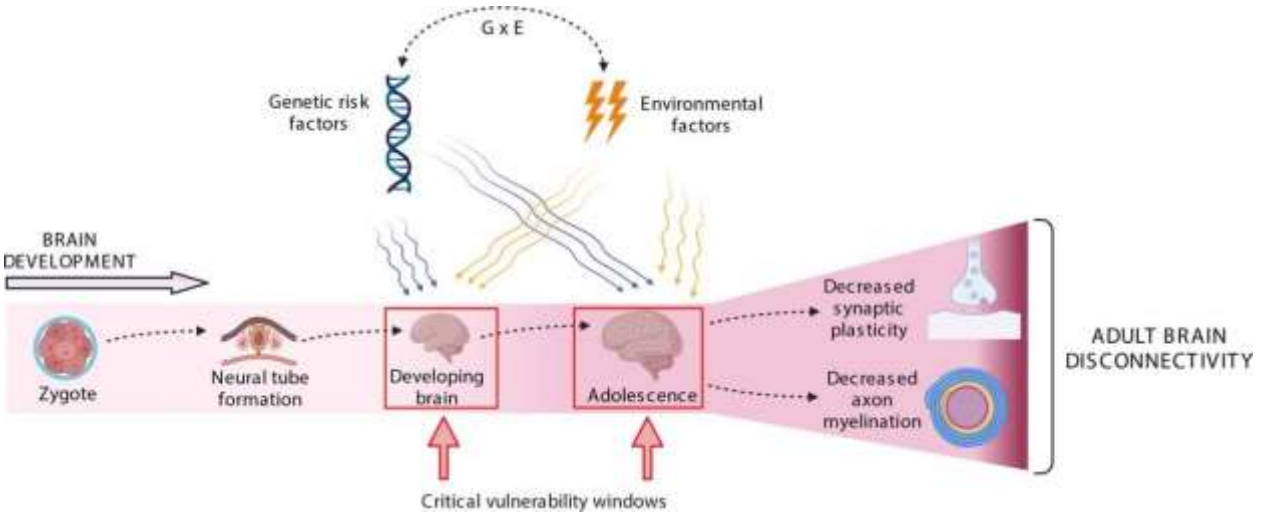


Figure 5. Neurodevelopmental "two-hit" model of schizophrenia illustrating how genetic susceptibility and environmental risk factors during prenatal development and adolescence disrupt synaptic plasticity and myelination. These abnormalities impair brain connectivity, leading to cognitive deficits and the emergence of schizophrenia symptoms in early adulthood.

Genetics and epigenetic mechanism

Schizophrenia is a highly heritable (70–80%) and polygenic disorder resulting from complex interactions between multiple susceptibility genes and environmental influences (113). Advances in genome-wide association studies (GWAS) have identified more than 100 genetic loci associated with schizophrenia, many of which regulate synaptic transmission, calcium signaling, glutamatergic neurotransmission, dopamine signaling, and immune function (114,115). Shared genetic variants with bipolar disorder, major depressive disorder, and autism spectrum disorder further indicate overlapping biological pathways. Among the most important susceptibility genes are DISC1, COMT, DRD2, DTNBP1, NRG1, RGS4, PPP3CC, ZDHHC8, AKT1, G72/G30, TRAR4, and the α7 nicotinic acetylcholine receptor, which influence neuronal development, synaptic plasticity, and dopaminergic and glutamatergic signaling (113,114). Variants within the major histocompatibility complex (MHC) further implicate immune and inflammatory mechanisms in schizophrenia development. MHC class I molecules regulate synapse formation, neurite outgrowth, and neuronal plasticity, highlighting the interaction between immune and neurodevelopmental pathways (115–117). Although GWAS has greatly improved understanding of schizophrenia genetics, translating these findings into early diagnosis and targeted therapies remains challenging (117,118). The identification of endophenotypes, which are heritable biological markers linking genetic variation with clinical phenotypes, may facilitate future precision medicine approaches (113) (Table 2).

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Table 2. Risk of schizophrenia with genetic relatedness

Relationship	Approximate lifetime risk
General population	1%
First degree relative	10%
Sibling	8-10%
One affected parent	10-1 5%
Two affected parents	40-50%
Monozygotic identical twin	40-50%
Dizygotic fraternal twin	10-15%

Environmental factors

Despite its high heritability, schizophrenia frequently shows discordance among monozygotic twins, emphasizing the important contribution of environmental factors (119,120). Prenatal and perinatal complications, including maternal infections, obstetric complications, and fetal hypoxia, increase the risk of schizophrenia and may contribute to cognitive impairment later in life (122–126). These environmental insults likely interact with genetic susceptibility to influence disease onset. Growing evidence also implicates urbanization, socioeconomic deprivation, air pollution, and childhood trauma as significant environmental risk factors for schizophrenia (127–136). Individuals raised in urban environments generally exhibit a higher incidence of schizophrenia and poorer cognitive outcomes than those in rural settings. Likewise, exposure to childhood physical or emotional trauma is consistently associated with impaired cognitive development and an increased risk of schizophrenia, supporting a multifactorial model in which environmental exposures modify genetic vulnerability throughout neurodevelopment (128,137–143).

DIAGNOSIS

The diagnosis of schizophrenia is challenging because of its marked clinical heterogeneity, variable disease course, and overlap with other psychiatric disorders. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), diagnosis is based on characteristic clinical symptoms rather than definitive biological markers. Patients present with varying combinations of positive, negative, and cognitive symptoms, which may be preceded by a prodromal phase lasting several years before the first psychotic episode (144,145). Current diagnostic systems, including the DSM-5-TR and International Classification of Diseases (ICD-11), were developed to facilitate clinical decision-making, standardize research, and improve communication among healthcare professionals (146). Both systems require the presence of characteristic psychotic symptoms; however, they differ in diagnostic duration criteria. DSM-5-TR requires continuous signs of illness for at least 6 months, whereas ICD-11 requires symptoms to persist for 1 month or longer, enabling earlier diagnosis and intervention (147–151). Although both classifications recognize disturbances of self-experience, including thought withdrawal, thought broadcasting, and passivity phenomena, they remain primarily symptom-based and inadequately capture the biological complexity and clinical heterogeneity of schizophrenia

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(151,152). Despite recent advances, current diagnostic criteria have important limitations. They do not adequately incorporate neurocognitive dysfunction, neurodevelopmental abnormalities, genetic susceptibility, or emerging molecular biomarkers, all of which are increasingly recognized as integral components of schizophrenia. Genome-wide association studies identifying schizophrenia-associated loci and single nucleotide polymorphisms (SNPs) provide promising opportunities for biomarker-guided diagnosis and personalized medicine; however, these approaches have not yet been integrated into routine clinical practice (145–158).

THERAPEUTIC APPROACHES

Schizophrenia affects approximately 1% of the global population and remains one of the leading causes of psychiatric disability. Modern treatment aims not only to reduce psychotic symptoms but also to improve cognitive function, prevent relapse, minimize adverse effects, enhance psychosocial functioning, and promote long-term recovery and quality of life (159–163).

Targeting the redox balance: Growing evidence indicates that oxidative stress contributes to schizophrenia pathogenesis by promoting neuronal damage and impaired brain function (164,165). Patients frequently exhibit reduced glutathione (GSH) levels, increased protein oxidation, and altered antioxidant enzyme activity, including glutathione peroxidase (GPX) and glutathione reductase (GR) (166,167). Experimental depletion of brain GSH produces schizophrenia-like cognitive deficits in animal models (168,169). Consequently, N-acetylcysteine (NAC), a precursor of glutathione, has emerged as a promising adjunctive therapy. NAC restores antioxidant capacity, reduces oxidative stress, improves electrophysiological abnormalities, and has demonstrated efficacy in alleviating negative symptoms of schizophrenia (170–175).

Targeting the glutamatergic pathway: N-methyl-D-aspartate receptor (NMDAR) hypofunction is considered a central mechanism in schizophrenia pathophysiology (176). Reduced NMDAR activity impairs parvalbumin-positive interneurons (PVIs) within the prefrontal cortex (PFC), leading to cortical disinhibition and disruption of the excitation–inhibition balance (177–180). Genetic studies have further identified schizophrenia-associated mutations in GRIN2A and GRIN2B, which encode NMDAR subunits (178). In addition, decreased expression of glutamic acid decarboxylase (GAD67) supports the involvement of impaired GABAergic neurotransmission in schizophrenia (181–183). Therapeutic strategies targeting glutamatergic dysfunction have shown encouraging results. Quercetin, a naturally occurring flavonoid that negatively modulates GABAA receptors, has been shown in experimental models to restore glutamatergic transmission, improve prefrontal cortical function, and reduce schizophrenia-like positive symptoms by enhancing the activity of dysfunctional parvalbumin interneurons (184,185).

Targeting the cholinergic system: Cholinergic dysfunction is increasingly recognized as an important contributor to schizophrenia. Neuronal nicotinic acetylcholine receptors (nAChRs) are expressed on both excitatory neurons and GABAergic interneurons, and altered α7 nAChR expression has been associated with impaired auditory sensory gating in patients with schizophrenia (186,187). Muscarinic

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receptors, particularly the M1 subtype, are widely distributed throughout the brain and play essential roles in cognition and synaptic plasticity. Clinical studies have shown that the anticholinergic agent trihexyphenidyl, which acts on M1 receptors, can alleviate certain negative symptoms (188,189). Cholinergic signaling also regulates dopaminergic neurotransmission through interactions between cholinergic interneurons and dopaminergic neurons within the basal ganglia. Activation of nAChRs enhances glutamate release and stimulates dopaminergic neurons in the ventral tegmental area, indicating that abnormalities in nicotinic and muscarinic receptor signaling may contribute to psychosis and movement disorders in schizophrenia (190–193).

Neurotropic factor enhancement: The brain-derived neurotrophic factor (BDNF)-TrkB signaling pathway plays a critical role in neuronal survival, neurogenesis, synaptic plasticity, and the maturation of parvalbumin-positive GABAergic interneurons (194–196). Reduced expression of BDNF, TrkB, parvalbumin, and glutamic acid decarboxylase (GAD67) has been consistently reported in schizophrenia, suggesting impaired neuroplasticity (197–199). Natural compounds such as curcumin and Ginkgo biloba extract (GBE) have attracted interest because of their antioxidant and anti-inflammatory properties (200). Curcumin readily crosses the blood–brain barrier, suppresses inflammatory cytokines and oxidative stress, enhances BDNF expression, and has demonstrated beneficial effects on positive, negative, and cognitive symptoms in both preclinical and clinical studies (201–204) (Table 3).

Table 3. Emerging therapeutic strategies targeting non-dopaminergic pathways in schizophrenia

Therapeutic Approach	Mechanism of Action	Potential Benefits
Glutamate-Modulating Agents	Enhance NMDA receptor function using com- pounds like glycine, D-serine, and sarcosine	May improve cognitive deficits and negative symptoms by addressing NMDA receptor hypofunction (220)
Anti-Inflammatory Antioxidant Agents	Reduce oxidative stress and neuro inflammation through omega-3 fatty acids, N-acetylcysteine (NAC),and flavonoids	Could provide neuroprotection, improve mitochondrial and enhance cognitive and functional outcomes (221,222)
Hormonal and Endocrine-Based Therapies	Address hormonal dysregulation using outcomes, selective estrogen receptor female patients, by modulators (SERMs) and thyroid estrogen and thyroid hormone supplementation hormone levels (223,224)	May improve treatment receptor particularly in modulating

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Pharmacological classes and mechanisms: First-generation antipsychotics (FGAs) primarily exert their therapeutic effects through potent dopamine D2 receptor antagonism, effectively reducing positive symptoms of schizophrenia. However, strong D2 blockade is associated with a higher risk of extrapyramidal symptoms (EPS) and tardive dyskinesia (205,206). Common FGAs include haloperidol, fluphenazine, chlorpromazine, perphenazine, and zuclopenthixol, with typical daily doses of 2–10 mg for haloperidol and 5–20 mg for fluphenazine (207–209). Although FGAs remain effective, current treatment guidelines generally reserve them for patients with previous good response or when cost is a major consideration (Table 4).

Table 4. Major first generation antipsychotics

Drug	Potency	Primary receptor Target	Major clinical use	Major adverse effects
Chlorpromazine	Low	D2, H1, M1, α1	Acute psychosis, agitation	Sedation, hypotension, anticholinergic effects, weight gain
Haloperidol	High	D2	Acute psychosis, schizophrenia, delirium	Extrapyramidal symptoms, hyperprolactinemia
Fluphenazine	High	D2	Maintenance therapy, long-acting injectable formulations	EPS, tardive dyskinesia
Perphenazine	Intermediate	D2	Chronic schizophrenia	EPS, moderate sedation
Trifluoperazine	High	D2	Schizophrenia, sever psychosis	EPS, hyperprolactinemia
Thrioridazine	Low	D2, M1, H1	Limited use	Cardiac toxicity, sedation, anticholinergic effects

Second-generation antipsychotics (SGAs) combine moderate D2 receptor antagonism with 5-HT2A receptor blockade, providing comparable efficacy against positive symptoms while improving neurological tolerability and offering modest benefits for negative and cognitive symptoms (210,211). Consequently, SGAs are recommended as first-line pharmacological therapy in most international guidelines. A comparative summary of the clinical characteristics, mechanisms of action, and adverse-effect profiles of FGAs and SGAs is presented in Table 5 & 6.

Table. 5 Clinical characteristics and adverse effects of atypical antipsychotics

Agent	Clinical profile	Notable Adverse Effects
Risperidone/Paliperidone	Potent D2, 5-HT2A blockade; good for aggression (212,213)	Hyperprolactinemia, EPS (212,213)
Olanzapine	Broad receptor binding; superior	Weight gain, metabolic syndrome

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	efficacy (212,214)	(212,214)
Quetiapine	Sedating, mood-stabilizing (212,215)	Orthostatic hypotension, sedation (212,215)
Ziprasidone	Pro-cognitive, low metabolic risk (212,216)	QTC prolongation (212,216)
Lurasidone	Pro-cognitive, minimal weight gain (214,217)	Akathisia, nausea (214,217)
Aripiprazole/Brexipraz ole/Cariprazine	D2 partial agonists, serotonin modulation (213,218)	Akathisia (aripiprazole), insomnia (213,218)
Asenapine	Sublingual; good for mixed symptoms (213,219)	Oral hypoesthesia, taste alteration (213,219)

Table 6. Comparison of first-generation and second-generation mGPCR antagonists used in schizophrenia treatment

S.NO	Typical mGPCR antagonists (First Generation; FGA)	Atypical mGPCR antagonists (Second Generation; SGA)
Example	Haloperidol and Chlorpromazine	Clozapine, Olanzapine, and Risperidone
Mechanism of action	Primarily block dopamine D2 receptors, reducing dopaminergic activity	Block both dopamine D2 and serotonin 5-$HT_{2\ A}$ receptors, leading to a more balanced neurotransmitter modulation
Efficacy	Effective in reducing positive symptoms (hallucinations, delusions)	More effective for negative symptoms (apathy, social withdrawal) and cognitive impairment (228, 229); Clozapine is particularly useful for treatment resistant schizophrenia
Side effects	Extrapyramidal symptoms (EPS) such as tardive dyskinesia, dystonia, rigidity, and tremors are quite likely. Neuroleptic malignant syndrome (NMS), a serious, sometimes fatal illness marked by hyperthermia and autonomic dysfunction, can be brought on by prolonged use (225-227)	Increased metabolic side effects, including weight gain, insulin resistance, and cardiovascular problems, but a decreased chance of EPS (230). Because clozapine increases the risk of agranulocytosis, routine blood monitoring is necessary (231)
Other Considerations	Generally, more affordable but associated with poorer tolerability due to motor side effects	Preferred for long-term treatment due to better tolerability but requires monitoring for metabolic and hematologic adverse effects

CONCLUSION

Schizophrenia is a complex and multifactorial neuropsychiatric disorder resulting from interactions among genetic susceptibility, neurodevelopmental abnormalities, environmental factors, immune dysregulation, and disturbances in multiple

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neurotransmitter systems. Current evidence indicates that its pathogenesis involves interconnected abnormalities in dopaminergic, glutamatergic, GABA-ergic, serotonergic, and cholinergic signaling, together with impaired synaptic plasticity, excessive synaptic pruning, oxidative stress, mitochondrial dysfunction, and chronic neuroinflammation. Advances in molecular genetics, epigenetics, and neuroimaging have redefined schizophrenia as a disorder of disrupted neural circuits and altered brain connectivity rather than a simple neurotransmitter imbalance. Although antipsychotic medications remain the cornerstone of treatment and effectively control positive symptoms, they have limited efficacy against negative symptoms and cognitive deficits, highlighting the need for more effective therapeutic strategies. Emerging approaches targeting glutamatergic neurotransmission, muscarinic cholinergic receptors, trace amine-associated receptor 1 (TAAR1), neuroinflammation, oxidative stress, and synaptic dysfunction offer promising opportunities for disease modification. In parallel, advances in pharmacogenomics, biomarker discovery, artificial intelligence, and precision medicine are expected to improve early diagnosis, patient stratification, and personalized treatment. Future research should integrate genomic, transcriptomic, proteomic, metabolomic, and neuroimaging data to identify reliable biomarkers and develop mechanism-based therapies. Well-designed longitudinal studies and clinical trials will be essential to translate these discoveries into clinical practice. Ultimately, combining pharmacological treatments with cognitive rehabilitation, psychosocial interventions, and digital health technologies may improve functional recovery and quality of life. A deeper understanding of schizophrenia biology will facilitate the development of personalized, disease-modifying therapies that extend beyond symptom control toward long-term prevention and sustained recovery.

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