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The Confluence of Genetic Factors and Neurotransmitter Dysregulation in Schizophrenia: A Comprehensive Review

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Abstract

Schizophrenia is a psychiatric condition characterized by a profound mental illness that impairs an individual's capacity to function in both social and cognitive domains. Individuals diagnosed with schizophrenia display psychopathological symptoms that are categorized as positive, negative, and cognitive. According to some estimates, nearly 98% of people with schizophrenia have cognitive deficits and perform below their expected cognitive capacity, which depends on their premorbid intelligence and parental educational attainment. Schizophrenia affects approximately 24 million individuals worldwide, which translates to a prevalence rate of 0.32%, or 1 in 300 people. In the interim, the prevalence of the condition among adults is 0.45% or 1 in 222 individuals. The heritability of schizophrenia is widely recognized to be significant, ranging from 60% to 90%. As a result, identifying specific risk genes is crucial for comprehending this disorder's underlying causes and physiological mechanisms. The pathophysiology of schizophrenia involves the dysregulation of various neurotransmitters and their pathways; various environmental factors, and heredity are also associated with it. Dopamine and other neurotransmitters linked with it, like serotonin and glutamine, have been the main drug targets of schizophrenia. The purpose of this review is to offer a comprehensive understanding of the etiology, pathophysiological mechanisms, and manifestations of schizophrenia. Overall, there is still insufficient evidence to prove the underlying cause of the pathogenesis of schizophrenia. Nonetheless, it is important to recognize the unknown and unidentified reasons underlying schizophrenia.

Keywords: schizophrenia; mental disorder; psychosis; the genesis of schizophrenia

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Introduction

History and Epidemiology

Schizophrenia is a psychiatric condition with a debilitating mental illness that affects one's ability to operate in both the social and mental spheres. In 1896 Emil Kraepelin elucidated this mental disorder as *dementia praecox*. Later in 1911, Eugen Bleuler redefined it as the term *schizophrenia*. Bleuler, a Swiss psychiatrist, first used the word schizophrenia in 1908 (Hany et al., 2024). This disease was defined as a set of symptoms that, in Bleuler's perspective, were linked to a fundamental shift in how people perceived reality. Dementia praecox was a term used frequently before Bleuler's research and was believed to be early-onset dementia. Since the time of Bleuler's discovery, schizophrenia has undergone a tremendous change (Uno & Coyle, 2019). After release of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) in the year 1952, schizophrenia was officially established as a separate diagnostic category. Moreover, at present *The International Classification of Diseases, Eleventh Edition* (ICD-11) and the *Diagnostic and Statistical Manual of Mental*

Disorders, Fifth Edition, (DSM-5) outline the current diagnostic criteria for schizophrenia.

According to ICD-11 (World Health Organization [WHO], 2022) "schizophrenia is characterized by disturbances in multiple mental modalities, including thinking (e.g., delusions, disorganization in the form of thought), perception (e.g., hallucinations), self-experience (e.g., the experience that one's thoughts or behavior are under the control of an external force), cognition (e.g., impaired attention), volition (e.g., loss of motivation), affect (e.g., blunted emotional expression), and behavior (e.g., bizarre behavior)" (Gaebel et al., 2020). The characteristics of schizophrenia are moreover the main criteria of diagnosis, as per ICD-11 for 1 month any two of the above-mentioned symptoms must be experienced the majority of the time. Similarly, the publication of DSM-5-TR (American Psychiatric Association, 2022) defined current criteria for diagnosing schizophrenia, which require the presence of a minimum of a pair of the symptoms that follow: delusions, hallucinations, disordered thinking (speech), disorganized/catatonic behavior, or negative symptoms. Furthermore, these symptoms need to be actively present for about or more than just 1 month, and the significant impairment in functioning for about 6 months. DSM-5-TR also states that these symptoms shall not be a result of substance abuse or any medical conditions (Biedermann & Fleischhacker, 2016).

Symptoms, Causes, and Risk Factors

Schizophrenia is a psychiatric condition that disrupts an individual's cognitive processes, emotional responses, behavioral patterns, and perception of reality (Rahman & Lauriello, 2016). People with schizophrenia exhibit psychopathological symptoms classified as positive, negative, and cognitive (Table 1).

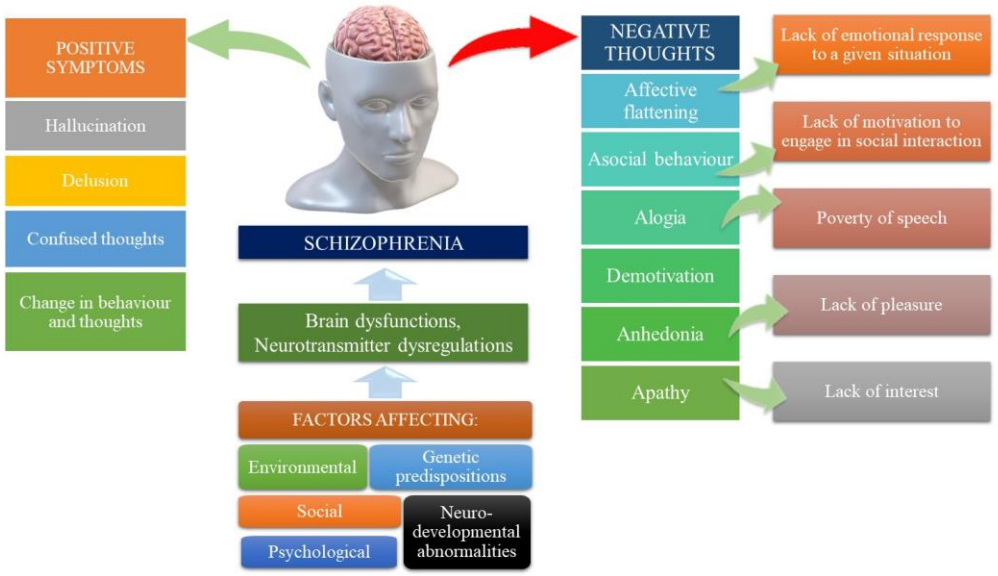
Table 1

Classification of the Symptoms of Schizophrenia

Category	Symptom	Characteristics	Reference
Positive	Hallucinations (e.g., auditory, visual)	Presence of abnormal experiences or perceptions	(Andreasen et al., 1994)
	Delusions (e.g., paranoid, grandiose)	Belief in false, irrational ideas or beliefs	
	Disorganized thinking and speech	Incoherent or illogical thought patterns	
Negative	Heightened emotions (inappropriate affect)	Expressing emotions not congruent with the situation	(Correll & Schooler, 2020; Mosolov & Yaltonskaya, 2022)
	Affective flattening (reduced emotional expression)	Restricted emotional range and lack of facial expressions	
	Alogia (poverty of speech)	Reduced speech output, minimal responses in conversation	
	Anhedonia (inability to experience pleasure)	Inability to derive pleasure from normally enjoyable activities	
	Avolition (lack of motivation)	Reduced motivation to initiate and sustain purposeful activities	
Cognitive	Social withdrawal and isolation	Avoidance of social interactions and withdrawal from relationships	(McCutcheon et al., 2023)
	Impaired memory and attention	Difficulty in maintaining attention, poor memory.	
	Impaired executive functioning (e.g., planning, organizing)	Difficulty in planning, decision-making, and organizing tasks	
	Impaired reasoning and problem-solving	Difficulty in logical reasoning and problem-solving	

Schizophrenia causes hallucinations that exhibit heterogeneity, encompassing a range of sensory modalities such as auditory, verbal, visual, olfactory, gustatory, and multimodal expressions, with auditory hallucinations being the most commonly reported (Llorca et al., 2016). Conceptually, an anomaly in functioning, such as delusional thoughts, hallucinations, or wildly disorganized thoughts or behavior, is regarded as one of the psychosis' positive symptoms (Khan et al., 2013). John Russell Reynolds described that negative symptoms are caused by the loss of "vital characteristics," which can lead to paralysis, anesthesia, and other abnormalities (Dollfus & Lyne, 2017). Typical negative symptoms include blunted affect, which refers to a reduction in emotional activity, anhedonia, which is characterized by an incapacity to encounter pleasure or joy, avolition (which is a lack of motivation), and apathy (which involves the suppression of emotion; Figure 1). Additionally, alogia (which is defined as a lack of speech) is also a common negative symptom.

Figure 1. *Factors Affecting and Symptoms of Schizophrenia.*



These symptoms are more prevalent than positive psychotic symptoms, vary less over time, and are significantly associated with poor psychosocial functioning. Patients are often seen as sluggish and deliberately disconnected by families and others because it is less evident that negative symptoms are signs of psychiatric disease (Wójciak & Rybakowski, 2018).

Based on premorbid intelligence and parental education levels, some estimates place the prevalence of these impairments in schizophrenia patients at close to 98%, which is below their projected cognitive function (Tripathi et al., 2018). A wide range of symptoms makes up this complex condition marked by mental, cognitive, and emotional stress. Schizophrenia affects approximately 24 million individuals worldwide, which equates to a prevalence rate of 0.32%, or 1 in 300 individuals. Conversely, the prevalence of the condition among adults is estimated to be 0.45% or 1 in 222 individuals (Patel et al., 2014). It is not as common as many other mental illnesses. Schizophrenia is known to be highly heritable (60–90%); therefore, identifying particular risk genes is essential for understanding its etiology and pathophysiology. Schizophrenia typically manifests during the late adolescent or early twenties period, with men experiencing its onset earlier than women. Individuals diagnosed with schizophrenia exhibit a significantly higher mortality rate, ranging from two to three times greater in comparison to the general population (Laursen et al., 2014). Until now, no particular cause has been identified for the progression of schizophrenia; however, researchers claim that multiple factors mentioned in Table 2, including physical, genetic, psychological, and environmental factors, contribute to this condition's development (Figure 1).

Table 2
Causes and Risk Factors Associated With Schizophrenia

Risk Factors	Causes	References
Genetic Factors	Family history of schizophrenia Specific genetic variations or mutations Complex genetic architecture, including common and rare genetic variants	(Trifu et al., 2020)
Neurobiological Factors	Neurotransmitter imbalances (e.g., dopamine, serotonin, glutamate) Structural brain abnormalities (e.g., enlarged ventricles) Altered brain function (e.g., impaired connectivity)	(Ross et al., 2006)
Prenatal and Perinatal Factors	Complications during pregnancy or birth Maternal infections, malnutrition, exposure to toxins, or stress	(Meli et al., 2012)
Psychological and Environmental Stressors	Severe stress or trauma during childhood or adolescence	(Stilo et al., 2011)
Childhood Trauma	Experiences of abuse, neglect, or trauma in childhood	(Popovic et al., 2019)
Cannabis Use	Heavy and frequent cannabis use during adolescence Particularly in genetically predisposed individuals	(Patel et al., 2020)
Infections and Immune Factors	Exposure to certain infections during pregnancy or early childhood Autoimmune conditions affecting the brain	(Benros & Mortensen, 2019)
Substance Abuse	Use of psychoactive substances (e.g., amphetamines, hallucinogens) Potential for triggering psychotic symptoms	(Khokhar et al., 2018)
Social Isolation	Lack of social support and social isolation	(Fulford & Holt, 2023)

Schizophrenia is characterized by widespread abnormalities across the brain. Notably, the inferior parietal lobule, superior temporal gyrus, prefrontal cortical areas, amygdala, medial basal ganglia, temporal lobe, corpus callosum, thalamus, and cerebellum exhibit the most persistent neurological changes (Tripathi et al., 2018). Increased awareness of mental health has facilitated the recognition and acceptance of mental disorders, including schizophrenia. Schizophrenia is a complicated and enigmatic disorder that is often subject to misinterpretation and widespread misconceptions.

Pathophysiology

Schizophrenia's pathophysiology entails the dysregulation of various pathways linked to brain function. The pathway is characterized by deviations in neurotransmission levels, either in the form of excessive or insufficient activity. Schizophrenia is characterized by alterations in the dopaminergic, glutamatergic, and γ-aminobutyric acid (GABA)ergic neurotransmitter systems, and the interactions between these receptors are implicated in the underlying pathophysiology of the disorder (Uher et al., 2019).

It has been observed that stimulants of the central nervous system, including amphetamines, increase dopamine release and induce psychotic symptoms. Similarly, positron emission tomography (PET) results of schizophrenia patients demonstrated enhanced dopamine activity in the striatum and midbrain regions of the brain (Howes & Kapur, 2009; Yang & Tsai, 2017). Studies conducted with the aid of PET imaging have demonstrated that schizophrenic patients manifest an elevated level of subcortical synaptic dopamine content (Kesby et al., 2018). The observation that heightened dopamine release is a fundamental factor contributing to psychotic symptoms has led to the inference that dopaminergic pathways represent the primary etiology of psychosis in individuals with schizophrenia (Stahl, 2018). The emergence of the D2 dopamine receptor (DRD2) gene has garnered attention. DRD2 is a transmembrane receptor that is a member of the G protein-coupled family and elicits intracellular signaling by impeding cyclic adenosine monophosphate (cAMP) synthesis (González-Castro et al., 2016).

Schizophrenia's etiology is believed to entail abnormal brain activity, particularly mesocortical dopamine levels. According to the glutamate theory, an excess in this neurotransmitter might result in motor symptoms that include agitation and restlessness (Egerton et al., 2020). Decreased activity of the dopaminergic system can also cause unpleasant symptoms, including anhedonia and apathy, which can lead to the onset of symptoms. The brain is comprised of four primary dopaminergic pathways, and it is hypothesized that schizophrenia's functional symptoms may be linked to reduced levels of mesocortical dopamine (Taylor et al., 2021).

Studies have demonstrated that individuals with heightened schizophrenia symptoms exhibit a greater likelihood of possessing mutations in genes associated with energy metabolism, such as the catechol-O-methyltransferase (COMT) gene (Wawrzczak-Bargieła et al., 2023). Schizophrenia is also linked to mitochondrial dysfunction and changes in how glial cells express themselves (Ni & Chung, 2020). It's been suggested that the absence of the schizophrenia gene in the brain may influence the emergence of symptoms and cognitive difficulties. Postmortem brains from persons with schizophrenia have been shown to exhibit alterations in glutamate receptors and synaptic plasticity, which may replicate symptoms experienced by those with the condition (Uno & Coyle, 2019).

Dysregulation in Neurotransmitter Pathways

The pathogenesis of schizophrenia is significantly influenced by neurotransmitters, which function as signal transmitters in the brain by communicating with each other through chemical compounds. Chemical synaptic transmission is caused by the release of neurotransmitters from presynaptic neural cells to postsynaptic receptors. Dysfunction in neurotransmitter receptors or imbalances in neurotransmitter concentrations can be a primary etiological factor in a range of neurological conditions, including but not limited to schizophrenia, depression, Alzheimer's disease, and other disorders (Bansal & Chatterjee, 2021). There are numerous primary neurotransmitters (Table 3); for example, epinephrine, norepinephrine, dopamine, and serotonin in the central nervous system for the proper functioning of human behavior, emotions, and the pathophysiology of several disorders (Hany et al., 2024). Along with the neurobiological system of the body, neurotransmitters tend to control blood sugar levels. Dopamine, serotonin, acetylcholine, GABA, glutamate, and norepinephrine are all neurotransmitters implicated in schizophrenia's pathogenesis. Dopamine is the most extensively studied neurotransmitter, garnering the highest degree of attention, followed by glutamate,

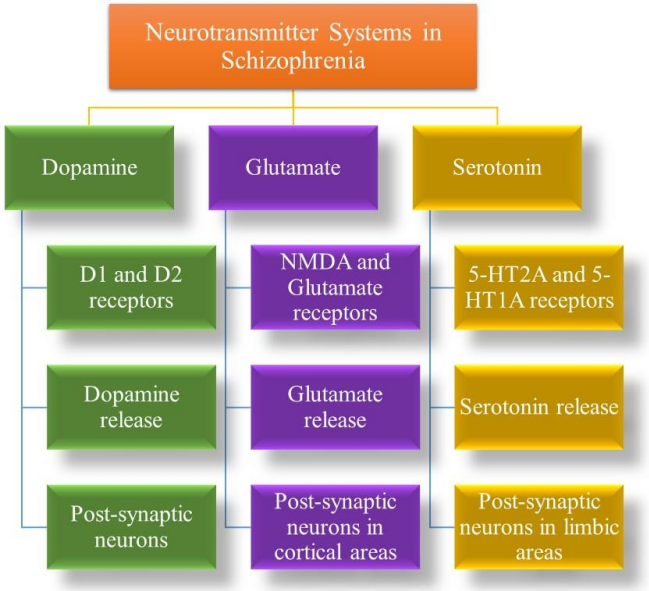
serotonin, GABA, and oxytocin. Schizophrenia has also been said to be linked with abnormalities in neuropeptides including neurotensin and cholecystokinin (Werner & Coveñas, 2010). The reason behind schizophrenia pathogenesis is because of dysfunctions in neurotransmitters like serotonergic alpha-adrenergic hyperactivity and dopaminergic hypoactivity (Figure 2).

Table 3
Neurotransmitters Involved in Schizophrenia

Neurotransmitter	Receptors	Implicated Brain Regions	Reference
Dopamine	DRD1 receptor, DRD2 receptor	Mesolimbic pathway (hyperactivity) and prefrontal cortex (hypoactivity)	(Luykx et al., 2017)
Serotonin	5-HT1A receptor, 5-HT2A receptor	Prefrontal cortex and limbic system	(Eggers, 2013)
Glutamate	NMDA receptor, AMPA receptor	Prefrontal cortex	(Hashimoto, 2011)
Gaba	GABAergic interneurons, GABA-A and GABA-B receptors	Prefrontal cortex	(Schoonover et al., 2020)
Acetylcholine	Muscarinic receptors (e.g., M1, M4) and nicotinic receptors (e.g., A7, α4β2)	Mesocortical pathway or the basal forebrain cholinergic system	(Jones et al., 2011)

It is believed that serotonin and glutamate may affect dopamine release, in the mesolimbic pathway there are dopamine neurons where 5-HT2A receptors are expressed thus by interacting with them serotonin contributes to dopamine activity (Stahl, 2018). Glutamate on the other hand interacts with N-methyl-D-aspartate (NMDA) receptors found on mesolimbic dopamine neurons. There is a chance that NMDA receptor hypofunction's activity is regulated by GABA hypoactivity and reduced glutaminergic activity (Kruse & Bustillo, 2022). Neurotransmitters have a significant impact on the maintenance of mental well-being, including the manifestation of schizophrenia as a mental disorder. Exploring the neurobiology of the neurotransmitter could facilitate the identification of the underlying etiology of schizophrenia and ultimately lead to the development of a viable remedy.

Figure 2. *Important Neurotransmitter Systems and Their Corresponding Receptors Highlight Their Contributions to the Network of Neural Signaling That Has Been Linked to the Development and Phenomenology of Schizophrenia*.



Dopamine

Dopamine's function (to transmit the signal along nerve fibers) makes it an important neurotransmitter, and its involvement in the dopamine hypothesis has become a popular researched theory of schizophrenia pathophysiology. Schizophrenic individuals often suffer from memory loss and thus fail to perform or contribute to the day-to-day chores. These are prominent symptoms of schizophrenia, caused because of disruptions in the dopamine pathway. Imaging studies of schizophrenic individuals' brains have an average of 5.8% increase in D2 receptors, which explains their behavioral hypersensitivity (Seeman, 2013). Since dopamine levels contribute to underlying symptoms, low levels of dopaminergic neurotransmissions in the brain may cause depression (Taylor et al., 2021). The enhanced level of dopaminergic neurotransmission in the mesolimbic pathway however is accountable for the manifestation of positive symptoms that include delusions and hallucinations (Stępnicki et al., 2018). Overactivity in the dopaminergic system can also cause disturbance in sleeping patterns in schizophrenic individuals (Ashton & Jagannath, 2020). Schizophrenic patients exhibit an elevation in the concentration of DRD2 within the striatum. Nevertheless, antipsychotic medications can be employed to manage this area. (Simpson et al., 2021).

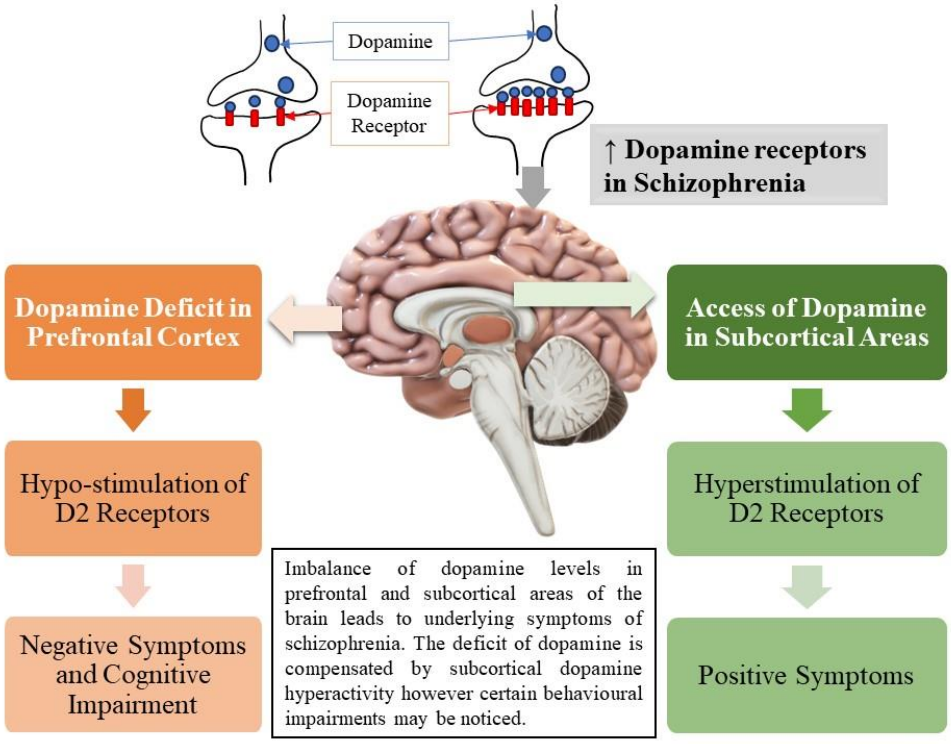
One of the principal treatments of schizophrenia includes antipsychotic medications that target and inhibit D2 receptors in the mesolimbic pathway, meanwhile reducing dopamine-related hyperactivity. In return, these medications tend to reduce the level of positive symptoms of schizophrenia, which gives more evidence for the pathophysiology of the condition (Bruijnzeel et al., 2014). Conversely, D1 receptors have a pivotal function in the regulation of dopaminergic transmission within the prefrontal cortex. Inadequate levels of D1 receptors may result in cognitive dysfunction and negative symptoms in individuals with schizophrenia (Howes & Kapur, 2009). By experimentally inducing striatal dopaminergic transmission, for example, administration of amphetamine can induce psychosis. Amphetamine acts on the dopamine neuron terminals, stimulating the release of higher levels of dopamine. This can elevate the likelihood of psychosis in individuals with schizophrenia, leading to the manifestation of positive symptoms associated with the disorder (Thompson et al., 2020). Enhanced (or imbalanced) transmission of dopamine in the mesolimbic pathway, which originates from the ventral tegmental area is assumed to be the main cause behind positive symptoms, which are supposed to initiate in the nucleus accumbent (Figure 3). Dysregulation of striatal dopamine signaling, which often has far-reaching implications on cortical function, may cause cognitive symptoms in people with dopamine

dysfunction, which are more commonly linked with positive psychotic symptoms (Simpson et al., 2021).

Serotonin

Another known neurotransmitter involved in the etiology of schizophrenia is serotonin (5-hydroxytryptamine or 5-HT). 5-HT surrounds the brain and is known to regulate mood, cognition, and perception. 5-HT in schizophrenia is responsible for causing negative and cognitive symptoms like apathy, anhedonia, and cognitive impairments (Pourhamzeh et al., 2021). There exist two contrasting theories regarding 5-HT regulating dopamine: according to one, serotonin influences dopamine release, while the other states that it may inhibit the release of dopamine in the mesolimbic pathway. Dopamine neuron activity in the striatum, which is involved in motor control and reward processing, is influenced by serotonin. Hence, the motor symptoms of schizophrenia may appear because of the disrupted dopamine system caused by serotonin pathway defects (Rogers, 2010). The central nervous system and peripheral tissue exhibit 14 different subtypes of serotonin receptors categorized as 5-HTx. A known 5-HT receptor, 5-HT2A, is widely known to contribute to the neurobiology of schizophrenia (Kantrowitz, 2020). In the postmortem study of schizophrenic patients, it was observed that along with 5-HT activity, there were 5-HT receptors and serotonin transporter (SERT) expressions as well (Pourhamzeh et al., 2021). 5-HT2A is well found in pyramidal neurons, while some of the 5-HT2A has NMDA glutamate receptors in colocalized form (Meltzer et al., 2003). In schizophrenic patients, the cortical 5-HT2A receptor is often at decreased levels while the 5-HT1A receptor is at increased levels (Meltzer et al., 2003). In schizophrenic individuals, the binding of serotonin to 5-HT2A in the prefrontal cortex regions is quite strong compared to healthy individuals. Because of this strong binding, this interaction may contribute to some distressing symptoms and cognitive deficits in schizophrenia (Quednow et al., 2020). Despite numerous studies, the current state of evidence is inadequate to substantiate the contribution of serotonin to schizophrenia's pathophysiology. However, it is noteworthy that certain 5-HT receptors, specifically 5-HT3 and 5-HT6, may serve as promising therapeutic targets for ameliorating the cognitive deficits and negative symptoms linked with this disorder (Liu et al., 2020).

Figure 3. *Schizophrenic Patients Exhibit Imbalanced Levels of Dopamine Neurotransmitters and Increased Expression of Receptors, Which Are Linked to a Range of Symptoms*.



Glutamate

One of the popular excitatory neurotransmitters present in the brain is known as glutamate. Its action is known to be mediated through receptors such as kainite, amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and NMDA (Negrete-Díaz et al., 2022). The glutamate pathway starts from its synthesis by neurons, after synthesis, it is released into the brain from where glial cells take it up and transform it into glutamine so that it can be delivered back to the neurons for further synthesis (Nedergaard et al., 2002). This glutamate–glutamine cyclic pathway is quite important for maintaining glutamate homeostasis in the brain. While investigating schizophrenia pathophysiology different deviations of the glutamatergic system have been identified such as glutamate level variations, and changes in receptor expression and function. Subsequent decreases in the expression of NMDA receptors (NMDAR) and lower glutamate levels within various brain regions including the prefrontal cortex and hippocampus were reported in the postmortem examinations of schizophrenic sufferers (Padmanabhan & Keshavan, 2014). Decreased NMDAR expression and disrupted glutamate levels are associated with negative symptoms and cognitive deficit which are characteristic symptoms of schizophrenia, these may include apathy and anhedonia. However, positive symptoms like hallucinations and delusions are also expected to be an output of disruption in the glutamate system in schizophrenic individuals (Mei et al., 2018). According to (Homayoun & Moghaddam, 2007) theory, schizophrenia-induced psychosis could be attributed to the hypofunctional NMDAR that are located on GABA interneurons within the cerebral cortex. This hypofunction can result in excessive stimulation of downstream glutamate signaling and an excess of dopamine within the ventral tegmental and ventral striatum via the mesolimbic pathway. It was observed that schizophrenic patients might have high activity of glutamate within some brain areas at the developing stage of schizophrenia while at the progressing stage of schizophrenia, there might not be enough glutamate activity (Stahl, 2018). Some authors believe that if schizophrenia is caused by glutamates, then the dopaminergic system modulates the secretion of glutamate or vice versa, leading to the onset of schizophrenia symptoms. However, the symptoms might be different for example glutamate may cause negative while dopamine can cause positive symptoms (McCutcheon, Marques, et al., 2020).

Role of Neurotransmitter Receptors in Schizophrenia Pathophysiology and Treatment

To develop novel treatment methods to treat schizophrenia, it is crucial to comprehend the various underlying targets. Hyperactivation, disruption, and poor functioning of multiple brain networks, neurotransmitters, receptors, signaling pathways, and proteins may be a reason for the pathophysiology of schizophrenia. Studies indicate that schizophrenia primarily affects the dopaminergic and glutamatergic brain circuits.

Dopamine Receptor Inhibitor

The first antipsychotic drug against schizophrenia is chlorpromazine, discovered by French Navy anesthesiologist Henry Laborit (Sushilkumar et al., 2022). After the breakthrough discovery of chlorpromazine as a therapy for schizophrenia, the mesolimbic dopamine pathway in dopamine dysfunction has been a major focus for researchers (Boyd-Kimball et al., 2018). “Cariprazine, brilaroxazine (RP5063), F17464, lumateperone (ITI-007), brexpiprazole, and lu AF35700 (Table 4) are examples of new novel substances that primarily impact dopaminergic receptors but also have some action on serotonergic receptors” (Lobo et al., 2022). Among these inhibitors, cariprazine functions as dopamine D2 and D3 receptor agonist, exhibiting greater efficacy in addressing negative and cognitive symptoms of schizophrenia due to its heightened affinity for D3 receptors (Laszlovszky et al., 2021). F-17464 is another compound that exhibits a greater binding affinity towards D3 receptors (Cosi et al., 2017). Clozapine, a second-generation schizophrenia treatment, is the best drug because clozapine balances dopamine and serotonin, improving mood, thinking, and behavior (Siskind et al., 2016). All contemporary antipsychotics function by either antagonizing or stabilizing dopaminergic receptors using D2/D3 partial agonists; one such example is aripiprazole (Molitch, 2020; Strange, 2008).

Table 4
Potential Novel Compounds That Modulate the Dopaminergic System

Substance	Targets	Clinical Trial Phase	Reference
Cariprazine	Partial agonist D2 and D3, 5-HT1A, an antagonist at 5-HT2B, 5HT2A, H1, 5HT2C, α1 (low affinity)	Phase 3	(Garnock-Jones, 2017)
Brexpiprazole	5-HT1A, D2, D3 partial agonist, 5-HT2A, 5-HT2B, 5-HT7, α1A, α1B, α1D, α2C antagonist	Phase 3	(Hsu et al., 2017)
Brilaroxazine (RP5063)	D3 antagonist 5-HT1A partial agonist	Phase 2	(Bhat et al., 2018)
F-17464	Partial agonist D2, D3, D4, 5-HT1A and 5-HT2A antagonist 5-HT2B, 5-HT2C, 5-HT6 5-HT7	Phase 2	(Bitter et al., 2017)
Lu AF35700	Antagonist at 5HT2A, 5HT2, D1	Phase 3	(Fellner, 2017)

5-HT Receptor Inhibitors

The serotonin hypothesis is primarily concerned with the interaction of a hallucinogenic chemical LSD (lysergic acid diethylamide) and 5-HT. The psychotogenic effects of LSD, as well as the antipsychotic benefits of serotonin-dopamine inhibitors that include clozapine and risperidone, have piqued researchers' attention in the interplay of these two neurotransmitters as potential pathophysiological targets in schizophrenia (Yang & Tsai, 2017). Cariprazine, as previously stated, is an agonist for both dopamine and 5-HT receptors, as well as a partial agonist for 5-HT1A and an antagonist for 5-HT2B receptors (Citrome, 2016). According to Satiamurthy et al. (2023), tropisetron, ondansetron, and granisetron have been identified as potential adjunctive treatments for cognitive and negative symptoms. Ondansetron, an antagonist of the 5-HT3 receptor, is often prescribed to cancer patients experiencing nausea and vomiting as a result of chemotherapy. It may also be associated with an anti-inflammatory therapy for schizophrenia and has undergone Phase 3 trials for the treatment of schizophrenia's negative symptoms (Tsitsipa et al., 2022). The newly approved antipsychotic lurasidone is a strong antagonist of SERT type 5 (SERT5), which may have therapeutic significance for the affective aspects of psychosis (Citrome, 2011; Yang & Tsai, 2017).

Glycine Type 1 Inhibitors

During the latter half of the 1990s, a growing body of evidence indicated that the hypoactivity of NMDAR could be a cause of schizophrenia pathophysiology (Balu, 2016). The glycine type 1 (GlyT1) receptor is a molecule with a vital role in the central nervous system. The glycine-type transporters have been recognized as pivotal regulators of glycine concentrations, which govern the functioning of NMDAR in collaboration with D-serine. As a result, GlyT1-mediated transport has become a novel target for the treatment of schizophrenia, prompting the development of high-affinity inhibitors (Shahsavar et al., 2021). The purpose of developing a GlyT1 inhibitor is to enhance the NMDAR-mediated neurotransmission in schizophrenia. Two such inhibitor examples, sarcosine (N-methyl glycine) and RG1678 (a high-affinity compound), are being studied in clinical trials. The prototype GlyT1 inhibitor, sarcosine, has exhibited favorable outcomes for negative and positive symptoms among individuals diagnosed with schizophrenia. Biopterin, a selective and noncompetitive GlyT1 inhibitor, has undergone clinical evaluation for treating negative and cognitive symptoms that have been linked with schizophrenia (Umbricht et al., 2014). After the second phase of clinical trials, the result showed that biopterin reduces negative symptoms which were measured by the Positive and Negative Syndrome Scale (PANSS; Pawlak & Zakowicz, 2022). Another GlyT1 inhibitor currently in the CONNEX program of Phase 3 trials for safety and efficacy evaluation that enhances glutamatergic activity and promises to improve cognitive symptoms in schizophrenia is BI 425809 (Rosenbrock et al., 2018). ORG-25935 is another example of a second-generation antipsychotic; it's a synthetic drug with the property of selective inhibition of GlyT1 since it

includes a residue of sarcosine (Castner et al., 2014). The progress toward the development of novel classes of GlyT1 inhibitors that are not derived from sarcosine was because sarcosine-derived GlyT1 inhibitors were exhibiting unwanted side effects, including ataxia (loss of complete control of bodily movements), hypoactivity, and decreased respiration (Peiser-Oliver et al., 2022).

N-methyl-D-aspartate (NMDA) Receptor and Schizophrenia

The pathophysiology of schizophrenia has been observed to involve a substantial role of NMDA neurotransmission hypofunction. The administration of NMDAR blockers, like phencyclidine (PCP) and ketamine, to individuals without schizophrenia has demonstrated the involvement of NMDAR in the pathogenesis of schizophrenia (Gozzi et al., 2007). The usage of antagonists revealed that healthy individuals exhibited negative and psychotic symptoms as well as cognitive impairment resembling schizophrenia symptoms (Adell, 2020). Several enzymes, such as D-amino acid oxidase (DAAO), which are not widely recognized, are important in the development of schizophrenia. As previously stated, D-serine functions as a coagonist at NMDAR, facilitating its catabolism (Cho et al., 2016). The condition of NMDR hypofunction arises due to reduced levels of D-serine in both the blood and cerebrospinal fluid (CSF). As per the findings (MacKay et al., 2019) there is an increase in the level of DAAO among individuals diagnosed with schizophrenia. This suggests that augmenting the levels of D-serine may enhance the functioning of NMDAR, resulting in the inhibition of DAAO. The compounds sodium benzoate and luvadaxistat TAK-831 (Devoe et al., 2019) are two promising novel DAAO inhibitors for alleviating symptoms of schizophrenia (Kuo et al., 2022). Memantine, also known as 1-amino-3, 5-dimethyladamanantate, functions as a noncompetitive partial antagonist of NMDA channel receptors. The administration of memantine has been observed to enhance both negative symptoms and cognitive deficits, with a specific emphasis on the negative symptoms associated with schizophrenia. This suggests that memantine, when used as supplementary therapy in schizophrenia, can effectively alleviate negative symptoms and cognitive deficits (Kikuchi, 2020).

Phosphodiesterase Inhibitors

Some of the novel compounds belonging to phosphodiesterase inhibitors have been studied for their potential in treating schizophrenia. These include BI409306 and phosphodiesterase 10A (PDE10A) inhibitors such as MK-8189, Roflumilast, and TAK-063 (Amin et al., 2021). The study conducted by (Layton et al., 2023), reveals that MK-8189 exhibits strong inhibitory effects on PDE10A and is being investigated as a promising candidate for a new antipsychotic agent. In mammals, PDE10A is strongly expressed and localized in the striatum. DE10A exhibits robust expression and localization within the striatum of mammalian organisms. The inhibition of PDE10A presents a new approach to restoring deficient striatal output, a key factor in the pathophysiology of schizophrenia (Layton et al., 2023). As per Menniti et al. (2007), the inhibition of PDE10A is capable of reducing positive symptoms of schizophrenia, boosting cognition, and addressing a few of the constraints of present medications by augmenting striatal cAMP and cGMP (cyclic guanosine monophosphate) signaling.

Cholinergic Receptors Inhibitors

According to Beck et al. (2015), nicotine, which is the main reinforcing element in tobacco, is believed to show a positive impact on the symptoms of schizophrenia, possibly due to the "self-medication" hypothesis. Alternatively, individuals with schizophrenia may experience increased rewarding effects from nicotine. Novel treatments for schizophrenia are currently under development, with potential targets such as nicotinic and muscarinic acetylcholine receptors (nAChRs and mAChRs). The mAChR M1 and M4 receptors and the 7-nAChR are increasingly being investigated as possible therapeutic targets (Jones et al., 2011). Clinical studies of schizophrenia patients have examined the use of agonists of 7-nAChRs as a supplementary treatment to antipsychotics in humans (Recio-Barbero et al., 2021).

Genetic Control of Neurotransmitter Pathways

There are several underlying factors behind the pathophysiology of schizophrenia which include genetic factors, environmental factors, and hereditary. From the genetics purpose, there is no particular one gene that may be directly responsible for schizophrenia, multiple genes are said to be causing the beginning and development of schizophrenia (Table 5). The central nervous system is majorly affected during schizophrenia, particularly in the regions of the frontal and temporal lobes which in turn affects memory, comprehension, and more. Numerous potential genes, including COMT, DISC1, RGS4, PPP3CC, ZDHHC8, AKT1, neuregulin, dysbindin, G72/G30, TRAR4, and alpha-7 nicotinic receptor genes, have been linked to schizophrenia. They are also involved in the

regulation of dopamine, a neurotransmitter associated with schizophrenia.

DISC1 Gene and Its Involvement in Neurodevelopmental Processes

The disrupted-in-schizophrenia 1 (DISC1) gene has been thoroughly investigated in schizophrenia, and cytogenetic studies conducted 20 years ago demonstrated the association between DISC1 gene deregulation and predisposition to schizophrenia (Blackwood et al., 2001). By disrupting presynaptic dopamine activity, the DISC1 gene seems to increase the likelihood of developing schizophrenia. According to studies, DISC1 changes are linked to enhanced amphetamine-induced dopamine release, which is correlated with amphetamine-induced positive psychotic symptoms seen in schizophrenia. The disruption of presynaptic dopamine control supports a function for DISC1 in modifying dopamine neurotransmission, despite the absence of obvious alterations in dopamine receptors. A meta-analysis of in vivo data in schizophrenia revealed no changes in dopamine D2/D3 receptor modifications, which is also consistent with the lack of observable changes in receptors (Dahoun et al., 2017).

COMT Gene and Its Impact on Dopamine Regulation

The dysregulation of glutamate elicits a compensatory response that triggers a subsequent dysregulation of dopamine. This dysregulation of dopamine leads to an increase in transcript levels of the COMT gene, which is situated at the 22q11 locus. The codon 158 of this particular gene encodes an enzyme that plays a role in the degradation of dopamine. The variability in the codon sequence has been observed to modulate enzyme activity. Specifically, valine has been shown to exhibit heightened activity, while methionine displays reduced activity. Consequently, the presence of valine is thought to be responsible for increased activity, which in further is linked with an elevated susceptibility to schizophrenia and disruptions in cerebral function (Trifu et al., 2020).

Table 5

Genes Involved in Schizophrenia Genesis

Gene Name	Gene ID	Chromosome	Function	Neurotransmitter System	Expression Pattern	Pathogenic Mechanism	References
ZNF804	91752	2q32.1	ZNF804A encodes zinc finger-binding protein.	glutamatergic neurotransmission	prefrontal cortex, hippocampus, and amygdala	Schizophrenia is linked to ZNF804A gene polymorphisms, specifically rs1344706.	(Wang et al., 2019)
PRODH	5625	22q11.2	PRODH encodes proline oxidase, which degrades proline.	glutamatergic neurotransmission	prefrontal cortex, hippocampus, and striatum	Dysregulation of PRODH and proline metabolism may affect synaptic plasticity, neurodevelopment, and oxidative stress, contributing to schizophrenia	(Clelland et al., 2014)
DISC1	27185	1q42.1	Gene regulates cortical and neurite outgrowth	dopamine, serotonin, and glutamate neurotransmission	hippocampus, prefrontal cortex, and striatum	DISC1 dysregulation disrupts neurodevelopmental processes such neuronal migration, synaptic plasticity, and dendritic spine shape, contributing to schizophrenia.	(Liu et al., 2019)
COMT	1312	22q11.21	Catabolizes catecholamine neurotransmitters including dopamine, norepinephrine, and adrenaline.	dopaminergic signalling	prefrontal cortex	Val158Met polymorphism, impacts prefrontal brain dopamine levels and may increase schizophrenia risk and cognitive impairment.	(Horikoshi et al., 2019)

Table 5
Genes Involved in Schizophrenia Genesis

Gene Name	Gene ID	Chromosome	Function	Neurotransmitter System	Expression Pattern	Pathogenic Mechanism	References
NRG1	3084	8p12	NRG1's membrane glycoprotein assists in intercellular communication and organ system development.	glutamatergic and dopaminergic neurotransmission.	prefrontal cortex, hippocampus, and striatum.	Schizophrenia may result from NRG1 signaling dysregulation.	(Vaht et al., 2016)
DTNBP1	84062	6p22.3	Involved in melanosome, platelet dense granule, and lysosome biosynthesis	glutamatergic and dopaminergic neurotransmission	hippocampus, prefrontal cortex, and striatum	DTNBP1 dysregulation impairs synaptic function, brain development, and neuronal connection, perhaps leading to schizophrenia.	(Domschke et al., 2011)
DRD2	1813	11q23.2	Facilitates the functionality of G protein-coupled receptors	dopamine neurotransmission	striatum, prefrontal cortex, and limbic system	Gene's missense mutations induce myoclonus dystonia and schizophrenia.	(Kaur et al., 2019)
5HTR2A	3356	13q14-q21	Codes for serotonin neurotransmitters	serotonin neurotransmission	prefrontal cortex, hippocampus, and striatum	Schizophrenia and OCD are linked to HTR2A gene mutations.	(Massoud et al., 2023)

Neuregulin 1 (NRG1) Gene and Its Role in Glutamatergic Signaling

Any disruption in brain development and neuronal transmission is associated with mental disorders including schizophrenia which is controlled by the gene neuregulin 1 (NRG1; Yang et al., 2020). Schizophrenia has been associated with genetic polymorphisms in the NRG1 gene, mostly in noncoding areas. These variants might control the expression of the NRG1 gene. Studies on the expression of NRG1 in schizophrenia patients' brains have produced inconsistent findings. While other research reveals higher NRG1 expression or greater NRG1 signaling in schizophrenia brains, some report reduced levels of NRG1 isoform 1 alpha. To properly comprehend NRG1's function in schizophrenia, more study is required (Wang et al., 2021).

Proline Dehydrogenase (PRODH)

Located on the 22q11 chromosome, the proline dehydrogenase (PRODH) gene is involved in the metabolism of L-proline, an amino acid thought to be important in glutamatergic neurotransmission. Although the precise mechanisms and connections are still being studied, dysregulation of the PRODH gene, particularly through overexpression of some variations, may affect glutamatergic pathways and contribute to the onset of schizophrenia (Yao & Han, 2022). Furthermore, a study conducted in Iran involving 360 participants has identified three polymorphisms located in the PRODH gene at positions 1766 A/G, 757C/T, and 1852 G/A. These polymorphisms are correlated with an increased chance of schizophrenia (Ghasemvand et al., 2015).

Dystrobrevin-Binding Protein 1 (DTNBP1)

The dystrobrevin-binding protein 1 (DTNBP1) gene, which produces the protein dysbindin-1, is situated on chromosome 6 at location 22.3. There are two coiled-coil domains in this conserved protein, which has about 350 amino acids. Dysbindin-1 comes in three different isoforms: dysbindin-1A, dysbindin-1B, and dysbindin-1C. Postsynaptic densities (PSDs) are the home of dysbindin-1A, synaptic vesicles are the main site of dysbindin-1B, and PSDs and synaptic vesicles are the home of dysbindin-1C. Dysbindin-1 plays a part in the control of the dopaminergic system and synaptic transmission in the hippocampus (Năstase et al., 2022), which is implicated in the pathophysiology of schizophrenia, according to experimental investigations using dysbindin-1 knockdown. Dysbindin-1B and dysbindin-1C levels in the hippocampus are decreased in schizophrenia patients, whereas dysbindin-1A levels are unaltered. Wang et al. (2017) suggest that different isoforms of dysbindin-1

showcase distinct biological functions in the context of schizophrenia.

Other Genes Linked with Schizophrenia

O'Donovan et al. (2008) in their first genome-wide study found a link between schizophrenia and polymorphism at position 804A of the ZNF804 gene that codes for the zinc finger protein. As per Nair et al. (2022) the trace amine receptor 4 (TAAR6) gene at location 6p23.2 is also identified as a candidate associated with schizophrenia. Epsin 4 located on chromosome 5q33 codes for a protein that controls neurotransmitter stability and transport and showed evidence of LD with schizophrenia (Tang et al., 2006). Even though autopsy studies have linked genes to schizophrenia, additional research is necessary to comprehend how genes affect the pathogenesis of the disease. To determine the efficacy of an antipsychotic drug, it is necessary to examine the SNPs (single nucleotide polymorphisms) of schizophrenia-associated risk genes. Future research on these SNPs could enable for more informed decisions regarding the optimal antipsychotic medication for specific patients.

Omics-Based Findings, Potent Therapies, and Drug Targets

The clinical heterogeneity of schizophrenia can now be better understood by researchers using genetic data. They intend to investigate how these genetic factors relate to symptom patterns, the likelihood of treatment response, and the clinical course of the disorder by assessing genetic liability in individuals, such as the number of common risk alleles, copy number variations (CNVs; Degenhardt, 2020), and exonic deleterious variations (Giusti-Rodríguez & Sullivan, 2013). Analysis of proteins and metabolites in schizophrenia sheds light on the intricate interactions between genetic, environmental, and developmental variables. Notably, these investigations demonstrate changed amino acids (glutamate, glutamine) and proteins (NEFL, GNB1, GLUL) in the glutamatergic system, suggesting its function in schizophrenia. Furthermore, schizophrenia has been connected to metabolic dysregulation, which is linked to reduced glucose tolerance and metabolic syndrome, highlighting the importance of altered energy metabolism in the condition (Guan et al., 2021).

Currently, treatments for schizophrenia are more focused on improving the cognitive deficits in the sufferers. Since symptoms of schizophrenia are not specific, according to the prognosis of the disorder, every schizophrenic individual goes through different sets of symptoms which makes it difficult to choose the right drug for treatment. Nevertheless, constant research is being made to develop antipsychotics, combinational therapeutics for the alleviation of schizophrenia. Therefore, there is always a possibility of encountering drawbacks, such as drug rejection, and the emergence of adverse effects such metabolic and cardiovascular issues, weight gain, mobility difficulties, and cognitive impairment as reported by Leucht et al. (2012). These adverse effects are attributed to the administration of antipsychotic medications, which have demonstrated efficacy in the management of schizophrenia. Diabetic patients are susceptible to weight gain due to the propensity of antipsychotic medications such as olanzapine, clozapine, and risperidone to induce weight gain. (Bansal & Chatterjee, 2021). The pharmacological approach along with cognitive remediations are the standard treatments for now. Early diagnosis of cognitive symptoms or any deterioration before it starts affecting lifestyle should be a concern and requires more research (Best & Bowie, 2017). A potential method for treating schizophrenia by modifying the affected neuronal circuits is provided by advanced and novel approaches like noninvasive brain stimulation (Gainsford et al., 2020), such as transcranial magnetic stimulation (TMS; Wu et al., 2022) or transcranial direct current stimulation (tDCS; Mondino et al., 2014). Another noninvasive brain stimulation targeting neuroplasticity—that includes transcranial stimulation electrically or magnetically, or stimulation of the vagus nerve—may be employed to target excitatory/inhibitory imbalance in schizophrenia (Blay et al., 2021; Markiewicz-Gospodarek et al., 2023).

Chronic schizophrenia, that shows no improvement even after medication, may also be managed with therapies with neuroplasticity potential like neurofeedback (NF) based treatments, and rehabilitation therapy with virtual reality and cognitive remediation (Markiewicz-Gospodarek et al., 2023; Surmeli et al., 2012). Although sample heterogeneity, NF training method, specific factors that drive NF outcomes, and experiments that evidently dissociate the different mechanisms that govern these outcomes are still the challenges being investigated, many successful attempts have been made using quantitative electroencephalography (qEEG) and quantitative event-related potentials (qERP; John et al., 1994; John et al., 2007; Surmeli et al., 2012). Other methods of biofeedback (BF) may be galvanic skin response (GSR-BF), electromyography (EMG-BF), and heart rate variability (HRV-BF; Markiewicz-Gospodarek et al.,

2023). These therapies have been successful in treating other neuropsychiatric conditions like thought disorders, personality disorders, behavioral disorders, depression and anxiety, drug-induced disorders, and dementia (Duric et al., 2023; John et al., 2007; Surmeli, 2014; Markiewicz-Gospodarek et al., 2023).

Effective drug targets still need to be researched, and there is a lack of evidence to understand schizophrenia's pathophysiology. For example, the role of serotonin in modulating symptoms of schizophrenia has been explained via dopamine regulation but its specific role is yet to be discovered. "Cariprazine, Brilaroxazine (RP5063), F17464, lumateperone (ITI-007), Brexpiprazole, and Lu AF35700 are a group of newly developed compounds that exhibit some impact on serotonergic receptors while primarily targeting the dopaminergic receptors" (Sparacino et al., 2022). Also, some drug development plans are targeting the NMDAR, as any deficits in this receptor contribute to cognitive impairments associated with schizophrenia. The potential use of memantine, a low-affinity antagonist of the NMDAR, has been identified for the management of positive symptoms and cognitive function (Kikuchi, 2020). The finding is significant because most NMDAR antagonists, together with PCP and ketamine, typically impair both symptoms and cognitive functioning in individuals with schizophrenia. (Frohlich & Van Horn, 2014). The investigation of the potential therapeutic effectiveness of cannabidiol (CBD) in the management of schizophrenia has been a topic of interest. Nevertheless, the findings from various studies have yielded inconclusive outcomes regarding the use of CBD as a treatment option for schizophrenia (White, 2019).

Conclusion

Schizophrenia originated from the Greek word "schizo" and "phren" meaning split mind and is characterized by a disrupted thought process, split personality, and distorted behavior. The precise cause of schizophrenia has been unidentified for over a century since it was first labeled in 1908. However, it appears that schizophrenia is developed because of an amalgam of genetic, environmental, and neurological variables. Currently, different research mentions the imbalance of neurotransmitters, particularly dopamine, serotonin, and glutamate, and their importance for the treatment of cognitive, negative, and positive symptoms. The prefrontal cortex, the hippocampus, and the thalamus are the main affected regions of the brain as neurotransmitters like serotonin, dopamine, and glutamate are respectively involved in there. These regions along with the action of the neurotransmitter play an essential role in a variety of cognitive functions which may include memory, thinking ability, problem-solving, movements, etc. The root cause not being known until now opens the door for more research on the pathophysiology of schizophrenia. Ultimately, schizophrenia is a complex and heterogeneous disorder involving numerous biological, psychological, and social factors. To thoroughly comprehend the mechanism, additional research is required.

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