Review

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Molecular Evidence Underlying Dopamine Hypothesis of Schizophrenia

Şizofrenide Dopamin Hipotezinin Moleküler Temelleri

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ABSTRACT

Schizophrenia is a chronic psychiatric disorder characterized by positive symptoms such as delusions and hallucinations, and negative symptoms like alogia and avolition. Affecting approximately 1% of the population, its etiology remains unclear, but it is believed to arise from the interaction of genetic and environmental factors, primarily impacting the frontal and temporal lobes. The dopamine hypothesis, a leading theory in explaining schizophrenia's pathophysiology, is based on observations that dopamine-enhancing substances like amphetamines can induce psychotic symptoms. Postmortem brain studies showing increased dopamine levels and D2 receptor density further support this hypothesis. Changes in D2R expression and dimerization are significant in schizophrenia's molecular basis. However, the dopamine hypothesis faces criticism due to inconsistencies between dopamine levels and symptoms, and the limited efficacy of antipsychotics in addressing negative and cognitive symptoms. Other neurotransmitter systems, including glutamate, GABA, and serotonin, also contribute to schizophrenia. Notably, NMDA receptor hypofunction is linked to neurodevelopmental and neurodegenerative processes. Genetic studies highlight variations in genes like ZNF804A, BDNF, and HLA as risk factors. Epigenetic mechanisms further influence gene expression, contributing to the disorder's pathophysiology. Schizophrenia requires a multifactorial model beyond dopamine dysfunction, with promising new treatments targeting glutamatergic, serotonergic, and immune pathways. This study discusses the validity of the dopamine hypothesis by reviewing molecular evidence and relevant findings from the literature.

Keywords: Schizophrenia, dopamine, dopamine receptors, serotonin, serotonin receptors

ÖZ

Şizofreni, sanrılar, varsanılar gibi pozitif semptomlar ile aloji, avolüsyon gibi negatif semptomları içeren kronik bir psikiyatrik bozukluktur. Toplumda yaklaşık %1 oranında görülen hastalığın etiyolojisi tam bilinmemekle birlikte, genetik ve çevresel faktörlerin etkileşimiyle frontal ve temporal lobları etkilediği düşünülmektedir. Dopamin hipotezi, şizofreninin patofizyolojisini açıklayan temel teorilerden biridir ve amfetamin gibi dopamin artırıcı maddelerin psikotik semptomları tetiklediği gözlemlerine dayanır. Postmortem beyin örneklerinde dopamin yoğunluğu ve D2 reseptörlerindeki artışlar bu hipotezi destekler. Şizofrenide D2R ekspresyonundaki değişiklikler ve dimerizasyon, hastalığın moleküler temelinde önemli rol oynar. Ancak, dopamin hipotezi, semptomlarla dopamin düzeyleri arasındaki tutarsızlıklar ve negatif/bilişsel semptomlarda antipsikotiklerin sınırlı etkisi nedeniyle eleştirilmektedir. Glutamat, GABA ve serotonin gibi diğer nörotransmitter sistemleri de şizofrenide rol oynar. Özellikle NMDA reseptör hipofonksiyonu, nörogelişimsel ve nörodejeneratif süreçlerle ilişkilendirilir. Genetik çalışmalar, ZNF804A, BDNF ve HLA gibi genlerdeki varyasyonların hastalık riskini artırdığını gösterir. Epigenetik mekanizmalar da gen ekspresyonunu etkileyerek patofizyolojiye katkıda bulunur. Şizofreni, dopamin disfonksiyonunun ötesinde, çok faktörlü bir modelle açıklanmalı; glutamaterjik, serotoninergik ve immün yolları hedefleyen yeni tedaviler umut vadetmektedir. Bu çalışma, dopamin hipotezinin geçerliliğini moleküler kanıtlara ve literatürdeki ilgili bulgulara dayandırarak tartışmaktadır.

Anahtar sözcükler: Şizofreni, dopamin, dopamin reseptörleri, serotonin, serotonin reseptörleri

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Introduction

Historical references to psychiatric symptoms resembling mood and psychotic disorders can be traced back to ancient Egypt. The Ebers papyrus, found in an ancient tomb and written in 1500 BC, is one of the most comprehensive sources unearthed by Georg Ebers in Thebes in 1872. In the Ebers Papyrus, mood disturbances were linked to cardiovascular dysfunctions; however, it is now understood that such conditions primarily originate in the brain. Schizophrenia, a chronic psychotic disorder, derives its name from the Greek words 'schizo' (split) and 'phrene' (mind), referring to the disconnection between thought and emotion (Karagülleoğlu et al. 2021). It is suggested that Schizophrenia, a psychiatric disease, has 4 basic symptoms: association, ambivalence, autism and affect. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) published by the American Psychiatric Association (APA), schizophrenia is a chronic psychiatric disorder characterized by persistent disturbances in cognition, perception, affect, insight, and behavior lasting for at least six months. Within this period, a minimum of one month must include active-phase symptoms such as delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. A diagnosis requires the presence of at least two of these core symptoms, one of which must be delusions, hallucinations, or disorganized speech. Additionally, the disorder must be associated with a marked decline in social, occupational, or interpersonal functioning (APA 2022).

The incidence of Schizophrenia is 1%, but it is 5–fold more common in those with low socioeconomic status than in those with high socioeconomic status. Schizophrenia occurs in men between the ages of 15-25, while it is seen in women between the ages of 25-35 (Summakoğlu and Ertuğrul 2018). Considering the clinical findings, it is divided into 5 subtypes: paranoid, disorganized, catatonic, undifferentiated, and residual according to the DSM-IV. In the paranoid type, delusions or hallucinations are seen, while disorganized speech and catatonic behavior are not present. In the disorganized type, disorganized speech and disorganized behavior findings are clearly present. Motor inactivity evidenced by catalepsy or stupor, excessive motor activity, excessive negativity (unmotivated resistance to all instructions) or mutism, oddities in voluntary movements, echolalia or echopraxia are the findings encountered in the catatonic type. The criteria for schizophrenia in the unspecified type are met, but since the symptoms do not meet the criteria for the Paranoid, Disorganized or Catatonic Type, schizophrenia patients are included in this group. The type in which there are no distinct delusions, hallucinations, disorganized speech or catatonic behavior, but there is evidence that the disorder continues, is classified as the Residual Type (Lykouras et al. 2001, Huang and Lee 2006, Korver-Nieberg N et al. 2011). However, in DSM-5, the validity of schizophrenia was questioned by removing the subtypes, and opinions were put forward to diagnose schizophrenia-related psychoses on a certain spectrum by evaluating their symptoms and severity (Mattila et al. 2015). With the publication of DSM-5, the traditional subtypes of schizophrenia were eliminated from the official diagnostic classification. This decision was primarily based on concerns regarding their limited diagnostic reliability, temporal instability, and lack of meaningful correlations with underlying etiology, treatment outcomes, or long-term prognosis (Tandon et al. 2013). Instead, DSM-5 encourages clinicians to adopt a dimensional assessment framework that evaluates symptoms across five core domains: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. This approach allows for a more comprehensive and clinically informative evaluation of the disorder's heterogeneous nature without relying on rigid categorical subgroups. Clinicians are further encouraged to use dimensional rating instruments—such as the Clinician-Rated Dimensions of Psychosis Symptom Severity—to quantify symptom severity and guide individualized treatment planning (American Psychiatric Association 2013). Antipsychotic medications form the cornerstone of pharmacological treatment for schizophrenia, though they are often supplemented with psychosocial interventions (Summakoğlu and Ertuğrul 2018).

The molecular mechanism underlying the pathology of schizophrenia is not completely understood, and antipsychotics used for treatment are only effective in half of the patients. Moreover, while they improve hallucinations or thought disorders, symptoms such as learning and attention disorders or social withdrawal cannot be treated. However, antipsychotics can cause significant side effects, including neurological and metabolic disturbances, as well as rare but severe reactions such as agranulocytosis,

especially with clozapine. G protein-coupled receptors (GPCR), which are dopamine, serotonin and adrenaline receptors, are the molecular targets of antipsychotics and show their effects on schizophrenia symptoms through these receptors (Stępnicki et al. 2018). More than 20% of patients with schizophrenia fail to respond to antipsychotic monotherapy, and 70% of patients may require lifelong drug therapy to control their symptoms. The findings in schizophrenia that monotherapy is not working have led clinicians to polypharmacy. Due to the risks associated with antipsychotic polypharmacy, it is generally recommended only after the failure of all monotherapy options, including clozapine. It has been argued that using clozapine with aripiprazole or D2 agonists may reduce side effects or residual symptoms, but there is still insufficient evidence (Lähteenvuo and Tiihonen 2021).

Epidemiological studies were generally found that the incidence of schizophrenia is equal in men and women, while symptoms are observed at an earlier age in men. While schizophrenia is more common in families with low socioeconomic levels, etiological studies have shown that schizophrenia is explained in genetic, neurodegenerative, neurodevelopmental and neurochemical models (Karakuş et al. 2017). Many genetic factors that contribute to schizophrenia have been proven in studies, but the one that is thought to contribute the most and is accepted to lie at the molecular basis of schizophrenia is the dopamine hypothesis. In this study, we aimed to explain the dopamine hypothesis and its deficiencies in schizophrenia, compare it with current hypotheses, and present the latest accepted understanding.

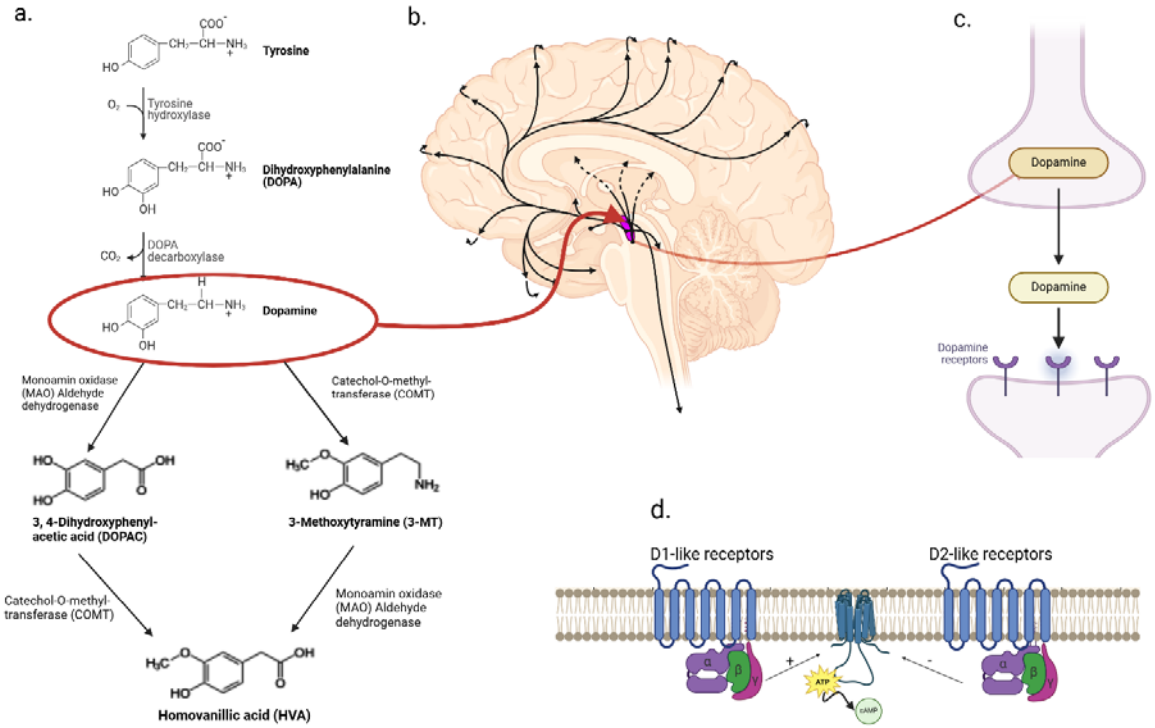

Figure 1. Dopamine synthesis, pathways and receptors

'a' shows the synthesis pathway of dopamine. 'b' shows the mesolimbic, mesocortical, and nigrastriatal pathways of dopamine produced from the VTA and substantia nigra. 'c' shows the presynaptic dopamine release and postsynaptic receptor localization in a dopaminergic chemical neuron. 'd' shows D1 and D2 receptors (Created in BioRender. Çaykara Peran, B. 2025. https://BioRender.com/k03a149).

Dopamine, its Production and Degredation

Dopamine (DA), a catecholamine neurotransmitter critical in reward and motor function in the central nervous system, is produced in the substantia nigra, hypothalamus, and ventral tegmental area (VTA). In the reward pathway, DA is produced in the VTA and released into the nucleus accumbens and prefrontal cortex. In the nigrostriatal pathway, DA is synthesized in the substantia nigra and released into the striatum (Juárez Olguín et al. 2016). Figure 1b illustrates the mesolimbic, mesocortical, and nigrostriatal pathways of DA originating from the VTA and substantia nigra. While the majority of DA synthesis occurs directly

from tyrosine, DA may also be synthesized indirectly from phenylalanine via converting L-phenylalanine to tyrosine by phenylalanine hydroxylase. In this synthesis, which takes place in two stages in the cytosol; tyrosine hydroxylase converts tyrosine to levodopa (L-DOPA) and L-DOPA is converted to DA by aromatic L-amino acid decarboxylase (DOPA decarboxylase). There is also a minor synthesis pathway in the substantia nigra where p-tyramine can be converted to DA via Cytochrome P450 2D6 activity. Following synthesis in dopaminergic neurons, DA can be stored in the acidic lumen of synaptic vesicles. In a non-acidic microenvironment, DA is converted to 3,4-Dihydroxyphenylacetaldehyde (DOPAL) by monoamine oxidase B (MAO-B) and subsequently converted to 3,4-dihydroxyphenylacetic acid (DOPAC) by aldehyde dehydrogenase (ALDH). DOPAC is converted to homovanillic acid (HVA) by catechol-O-methyltransferase (COMT), which can also directly convert DA to 3-methoxytyramine (Figure 1a). DA and its metabolites can be measured in the blood and cerebrospinal fluid; however, it is difficult to determine their exact origin due to production in both the central nervous system and peripheral organs such as the kidneys and intestines (Klein et al. 2019). Figure 1a shows the synthesis pathway of DA.

Dopamine Receptors

DA initiates intracellular signaling cascades upon binding to its receptors on the plasma membrane. DA receptors belong to a family of G protein-coupled receptors (GPCRs) with five subtypes and are divided into two main subgroups, D1-like (D1R, D5R) and D2-like (D2R, D3R and D4R), based on sequence similarities (Sun et al. 2021) (Figure 1d). Each DA receptor subtype (D1 through D5) has distinct functional roles and regional distributions in the brain. While almost all DA receptors are associated with memory and attention, D3R, D4R, and D5R have been implicated in cognitive processes (Mishra et al. 2018).

After DA binds to D1R, D1R binds to the intracellular heterotrimeric stimulatory G protein (Gs) with conformational changes. Thus, adenylyl cyclase is activated and the production of the secondary messenger, cyclic AMP (cAMP), begins and the signaling cascade is activated downstream. Furthermore, many GPCRs, including D1R, are also involved in non-canonical G protein-independent pathways. Activated D1R may undergo endocytosis by β-arrestin2, which may cause receptor loss on the cell surface (Gray et al. 2018).

D1R and D5R are coupled to stimulatory G proteins (Gs), which activate adenylyl cyclase, leading to the activation of protein kinase A (PKA) and subsequent regulation of gene transcription. D1R and D5R activate phospholipase C as well as stimulation of adenylyl cyclase, triggering intracellular calcium release and activation of protein kinase C (PKC). This calcium influx also contributes to the modulation of neurotransmitter release via exocytosis. D2R, D3R and D4R bind to G inhibitory domains that inhibit adenylyl cyclase activity. This results in the activation of K^+ channels, leading to potassium efflux and hyperpolarization of the membrane beyond the resting potential. These receptors also influence extrapyramidal activity mediated by the postsynaptic receptor. D2R, D3R, and D4R play crucial roles in signaling pathways that support dopaminergic neuron survival and development. D1R is the most abundant receptor in the central nervous system, followed by D2R, D3R, and D5R. The least abundant DA receptor in the central nervous system is D4R. D1 and D5 receptors are found in high density in the olfactory bulbus, nucleus accumbens, striatum, and substantia nigra, while D2, D3, and D4 receptors are expressed mainly in the striatum, external globus pallidus, amygdala, hippocampus, nucleus accumbens, and cerebral cortex (Vekshina et al. 2017, Mishra et al. 2018). Figure 1c schematically illustrates presynaptic DA release and postsynaptic receptor localization within a dopaminergic synapse and Figure 1d schematizes

Dopamine Hypothesis of Schizophrenia

Dopaminergic signaling pathways are crucial for maintaining physiological processes, and their dysfunction can lead to neurodegenerative and psychiatric disorders. Uncovering the molecular mechanisms of these diseases may contribute to the development of new treatments. There are many studies in the literature on the potential role of DA signaling pathways in triggering the onset and progression of some diseases in the nervous system, such as Schizophrenia, Parkinson's, and addictions (Klein et al. 2019, Channer et al. 2023). The DA hypothesis of schizophrenia emerged from indirect evidence,

including studies showing that administration of amphetamines and other compounds that increase extracellular DA levels can induce psychotic symptoms resembling those observed in schizophrenia. It was shown that some psychotic symptoms develop due to increased DA concentration and that these are similar to schizophrenia. It was discovered that the therapeutic efficacy of antipsychotic drugs correlated with their affinity for DA receptors, particularly in the context of altered DA receptor densities. Studies showed that an increase in both striatal DA levels and D2R density without causing changes in DA transporter (DAT) densities in post-mortem studies of patients with schizophrenia. Later studies provided more details regarding the nature of pre- and post-synaptic DA changes (Howes et al. 2015). One study showed that tyrosine hydroxylase involved in DA synthesis, was upregulated in the substantia nigra in schizophrenia, and based on this finding, they concluded that DA production capacity was increased in the midbrain and striatal terminals of DA neurons. (Howes et al. 2013).

The DA hypothesis, initially proposed to explain the pathophysiology of schizophrenia, currently presents several theoretical contradictions when evaluated in light of recent clinical findings and neurobiological data. One of the most significant issues is the lack of a consistent and direct relationship between DA levels and the manifestation of symptoms. For example, dopaminergic hyperactivity has been observed in some asymptomatic individuals, whereas certain patients with prominent positive symptoms have shown no significant alterations in DA synthesis (Howes et al. 2012). Another notable contradiction lies in the limited efficacy of classical antipsychotic medications, which primarily exert their effects through D2 receptor antagonism. While these agents are effective in reducing positive symptoms, they have consistently failed to produce meaningful improvements in negative and cognitive domains (Millan et al. 2012). Moreover, the DA hypothesis falls short in accounting for the developmental and cortical abnormalities observed in schizophrenia, many of which are more comprehensively addressed by disruptions in other neurotransmitter systems such as glutamate, GABA, acetylcholine, and serotonin (Moghaddam and Javitt 2012).

Additionally, it has been proposed that dopaminergic dysregulation may not represent a primary pathological mechanism of schizophrenia but rather a downstream consequence of broader neurobiological disturbances (Kaar et al. 2019). Collectively, these contradictions indicate that DA dysregulation alone cannot fully explain the complex clinical phenotype of schizophrenia. Instead, DA must be viewed as one component of a broader, multifactorial model that incorporates multiple interacting molecular and neural systems.

Dopamine Hypothesis, Dopamine Receptors and Neuroimaging Studies

A study in post-mortem samples showed that increased presynaptic D2R expression in the dorsolateral prefrontal cortex compared with controls, whereas decreased expression of predominantly postsynaptic variants. The results showed that D2R is altered in schizophrenia is supported by genetic findings and this led to the establishment of the hypothesis via showing a clear relationship between the D2R gene and schizophrenia (Kaalund et al. 2014). Studies have shown that DA receptors form dimers with themselves or with other receptors. There have been many studies examining the role that DA receptor dimerization may play in schizophrenia. A neuroimaging study has shown that D2/D3 receptor antagonism applied for seven days in healthy individuals causes negative symptoms. Partial D2/D3 agonism applied for the same periods of time was determined not to disrupt reward signaling or motivated behavior, and both applications cause motor disorders unrelated to the striatal reward response, suggesting that D2/D3 signaling may be effective in explaining the molecular mechanism of motivation and emotional responses in schizophrenia (Osugo et al. 2025).

Wang et al. found that there was a 278% increase of 15 schizophrenia patients in the expression of D2R dimers compared to controls, while D2R monomers decreased to 69% compared to the control (Wang et al. 2010). The high affinity of several antipsychotic drugs for the DA D3 receptor (D3R) has established this receptor as a pharmacologically relevant target (Sokoloff et al. 2006). The partial agonist activity of third-generation antipsychotics such as aripiprazole and cariprazine at D3R suggests that this receptor may

contribute to the therapeutic efficacy of these agents in addressing not only positive but also negative symptoms of schizophrenia (Gyertyan et al. 2011).

There is preliminary evidence for D2R heteromers from an autopsy study that found increased D1R-D2R heteromers in the globus pallidus in schizophrenia (Perreault et al. 2010). In a PET imaging study, D2R availability was found to be significantly increased in the group receiving long-term antipsychotic treatment; this result is consistent with the information that antipsychotic treatment causes D2R upregulation (Silvestri et al. 2000). Two studies examining chronic, drug-using patients showed widespread cortical and striatal reductions in D1R densities (Hirvonen et al. 2006, Kosaka et al. 2010). A study conducted on patients who had never used antipsychotics and had not received medication treatment showed a decrease in D1R prefrontal cortex densities (Okubo et al. 1997), while another study conducted on patients who had never used antipsychotics did not show any significant difference (Karlsson et al. 2002). Decreased expression of D1 receptors (D1R) in the dorsolateral prefrontal cortex of patients with schizophrenia has been particularly associated with negative and cognitive symptoms (Abi-Dargham et al. 2002). Findings from positron emission tomography (PET) studies demonstrating that D1R agonists enhance cognitive performance by modulating prefrontal cortex activity have identified D1R as a promising therapeutic target (Slifstein et al. 2007).

The high affinity of atypical antipsychotics—such as clozapine—for the D4 receptor (D4R) has suggested that these agents may be particularly effective in treatment-resistant schizophrenia cases (Van Tol et al. 1991); however, the considerable interindividual variability in D4R expression indicates that this effect cannot be generalized to the broader population (Oak et al., 2000). D5 receptors are predominantly expressed in the hippocampus, thalamus, and other limbic regions, and their neuroanatomical distribution implicates them in processes related to learning, motivation, and emotional regulation. In schizophrenia, reduced expression of D5 receptors (D5R) has been associated with negative symptomatology, particularly motivational deficits and affective flattening (Ciliax et al., 2000).

In conclusion, the contemporary DA hypothesis of schizophrenia emphasizes not just DA levels, but also the differential distribution, signaling properties, and dimerization behavior of receptor subtypes. These factors collectively influence the diverse symptom dimensions of schizophrenia, reinforcing the need for receptor-specific therapeutic approaches.

Findings on Relationship between Serotonergic System and Schizophrenia

The discovery that the radiotracers also bind to the 5HT2A receptor suggests that serotonin, in addition to DA, may be involved in the pathology of schizophrenia (Ekelund et al. 2007, Catafau et al. 2010). The mechanisms of action of atypical antipsychotics have revealed that the serotonergic system also plays a role in the etiology of schizophrenia. It is thought that the increased sensitivity of postsynaptic serotonin receptors causes some symptoms of schizophrenia (Yavaşçı and Akkaya 2012). Initially, brain serotonin receptors were classified into two subtypes: 5-HT1 and 5-HT2. However, subsequent biochemical studies have identified 14 serotonin receptors grouped into seven families (5-HT1 through 5-HT7) (McCorvy and Roth 2015).

Among the 5-HT1 receptors, 5-HT1A is the most extensively studied and is predominantly expressed in limbic structures. It is thought that the effect of atypical antipsychotics on improving cognitive problems in schizophrenia patients is due to the increase in DA release from the prefrontal cortex via 5-HT1A receptors. There are studies reporting that 5-HT1A receptors are responsible for cognitive changes in schizophrenia (Selvaraj et al. 2014). It is thought that the 5-HT2A receptor plays a role in the cognitive process of working memory, which is impaired in schizophrenia (Nocjar et al. 2002, Kim 2021). While serotonin has a suppressive effect on mesocortical DA neurons, the suppressive effect of serotonin is eliminated in 5-HT2 blockade, causing an increase in DA in the frontal lobe. 5-HT2 receptors are located presynaptically on dopaminergic neurons, and stimulation of these receptors with serotonin causes a tonic inhibitory effect and a decrease in DA release. It was shown that increasing DA through 5-HT2 blockade or another way reduces negative symptoms (Soykan and Şarman 1993). 5-HT2A and 5-HT2C receptors belong to the GPCR superfamily and have been shown to regulate a wide range of functions, such as depression,

schizophrenia, anxiety, sleep patterns, and feeding behavior (Van Oekelen et al. 2003). The two primary modulators of DA production are 5-HT2A and 5-HT2C receptors. Preclinical studies show that 5-HT2A receptor antagonists and/or 5-HT2C receptor agonists can effectively reduce craving and/or relapse and similarly promote withdrawal, while 5-HT2C receptor agonists can effectively reduce cocaine intake (Bubar and Cunningham 2006).

Glutamate Hypothesis, Neurodevelopmental and Neurodegenerative Model in Schizophrenia

From a psychological perspective, the DA hypothesis posits that subcortical DA release increases rapidly—within milliseconds—when novel potential rewards are encountered or when established reward-related associations are disrupted. Consequently, the dopaminergic system has been linked to reward processing and reinforcement. To account for long-term behavioral adaptations, the "motivational salience" hypothesis was introduced, proposing that stimuli are encoded as rewarding or aversive based on DA-mediated neural changes. These stimuli thereby acquire salience, guiding attention, motivation, and goal-directed action (Yüksel and Üçok 2010). It was suggested that psychotic symptoms seen in schizophrenia result from a distorted attribution of importance to external and internal stimuli. According to Kapur, the subcortical dopaminergic system, which is activated by internal or external stimuli and independently of the stimuli before psychosis, and antipsychotic treatment is effective by inhibiting the impaired attribution of importance (Kapur 2003). Antipsychotic drugs suppress dopaminergic activity, thereby reducing the salience of delusions and hallucinations and weakening their influence on behavior. However, since antipsychotic therapy does not fully reverse the underlying neurobiological abnormalities, symptoms often re-emerge upon dose reduction, discontinuation, or exposure to stressors (Yüksel and Üçok 2010).

Genetic predisposition and environmental factors are both implicated in the neurodevelopmental abnormalities observed in schizophrenia. The hypofunction of N-methyl-D-aspartate (NMDA) receptors is thought to play a central role in the pathophysiology of the disorder, contributing significantly to both neurodevelopmental and neurodegenerative processes. Specifically, reduced NMDA receptor activity has been linked to abnormalities in both early development and the progressive deterioration of neuronal circuits (Egerton et al. 2020). NMDA receptor hypofunction, particularly on parvalbumin-positive GABAergic interneurons, may lead to excessive glutamatergic activation and excitotoxicity, resulting in developmental anomalies such as excessive synaptic pruning, dendritic spine loss, and weakened neuronal connectivity (Steullet et al. 2017). Furthermore, genetic variations in glutamatergic pathway–related genes, including those encoding NMDA receptor subunits and metabotropic receptors, have been shown to significantly elevate the risk of developing schizophrenia (Egerton et al. 2020).

NMDA receptor hypofunction is proposed as a mechanism driving progressive neuronal damage in neurodegenerative model. Reduced NMDA activity may lead to increased extracellular glutamate, oxidative stress, and microglial activation, collectively contributing to neuronal loss and the worsening of negative symptoms. Additionally, glutamate dysregulation may impair astrocyte function, thereby exacerbating both developmental and degenerative pathological processes in the brain (Vellucci et al. 2025). The limited efficacy of current antipsychotic treatments, especially on cognitive and negative symptoms, has prompted increasing interest in targeting the glutamatergic system. In particular, metabotropic glutamate receptor 2/3 (mGluR2/3) positive allosteric modulators (PAMs) have emerged as promising therapeutic candidates due to their potential to restore synaptic integrity in the context of NMDA receptor dysfunction (Egerton et al. 2020).

Recent In Vivo and Postmortem Findings Related to Dopamine and Schizophrenia

In vivo studies show that there is an increase in synaptic density in the early stages of development, synaptic elimination occurs after adolescence until early adulthood, and synaptic density remains stable in adulthood (Drzewiecki et al. 2016). Findings from human postmortem tissues have also determined that

synaptic density in early childhood gradually decreases towards the age of 30 (Petanjek et al. 2011). During these neurodevelopmental processes, significant changes occur in the cortical excitation-inhibition (E/I) balance (Dorrn et al. 2010). It was shown that elimination, one of the synaptic modifications mediating these processes, is provided by microglia (Paolicelli et al. 2011). Microglia identify synapses destined for elimination via specific molecular tagging mechanisms. Mice overexpressing one of these molecular markers, complement factor 4A (C4A), were found to have their synapses eliminated by microglia, resulting in decreased cortical synaptic density and behavioral changes (Yılmaz et al. 2021). Furthermore, microglial elimination and synaptic loss have been shown to be greater in men than in women, and even chronic stress leads to microglial elimination in men. These findings help explain the knowledge that schizophrenia occurs earlier in men than in women (Howes and Shatalina 2022).

Chen et al. identified synaptotagmin-11 (Syt11) as a potential genetic risk factor for schizophrenia and showed that Syt11 deficiency in DA neurons in early adolescence leads to DA over-transmission, leading to persistent social deficits and schizophrenia-like behaviors (Chen et al. 2024). Decreased striatal DA transporter (DAT) and decreased phenylalanine, tyrosine, leucine, and isoleucine levels have been demonstrated in patients with schizophrenia, and low DAT in the left caudate nucleus or putamen was found to be positively correlated with attention deficit (Yang et al. 2024). In addition to oxidative stress and neuroinflammation resulting from mitochondrial defects, defects in the enzymes involved in DA catabolism have also been found to be associated with schizophrenia (Xu and Yang 2022).

In conclusion, it is thought that pruning by microglia regarding synapse formation or elimination during the neurodevelopmental phase may negatively affect homeostasis under various genetic variations and environmental influences, leading to the loss of glutamatergic synapses in the frontal cortical region, which may play a role in the manifestation of psychotic symptoms by creating changes in DA levels by inhibiting the excitatory projections regulating mesostriatal DA neurons.

Recent Findings Related to NMDA, GABA and Schizophrenia

In vivo studies have demonstrated that mesostriatal dopaminergic neurons are regulated by excitatory projections from the frontal cortex. Lesions in the frontal cortex have been shown to increase DA levels in the striatum (Howes and Shatalina 2022). When the medial prefrontal cortex is stimulated by optogenetic methods, excitatory afferents, cholinergic and glutamatergic systems are activated, leading to striatal DA release (Quiroz et al. 2016). Furthermore, progressive cortical synaptic loss has been found to lead to hyperlocomotion and increased striatal DA in a mouse model (Kim et al. 2015). While the presynaptic effects of DA on primitive cells and interneurons reduce neurotransmitter release, postsynaptically it may increase the excitability and firing of these neurons and affect E/I balance (McCutcheon et al. 2023). Glutamatergic inputs from the frontal cortex modulate DA neuron activity. Cortical pyramidal glutamatergic projections excite inhibitory gamma-aminobutyric acid (GABA) interneurons, GABA release from interneurons decreases the firing rate of cortical glutamate neurons and affects the firing of dopaminergic neurons in the mesolimbic pathway. A decrease in NMDA receptor (NMDAR) function in GABAergic interneurons may result in decreased inhibitory effects on glutaminergic neurons, increasing the firing of these neurons and leading to increased striatal DA and associated positive symptoms. This has been called the 'NMDA receptor hypofunction hypothesis' (Buck et al. 2022).

Mice treated with an NMDAR antagonist such as ketamine exhibit dehyperlocomotion, locomotor sensitivity and increased striatal DA synthesis (Kokkinou et al. 2021). Low N-acetylaspartate levels in the dorsolateral prefrontal cortex have also been associated with greater striatal DA release in schizophrenia, and since low N-acetylaspartate levels are associated with neuronal dysfunction, frontal neuronal function has been inferred to be impaired (Whitehurst et al. 2020). Recent studies suggest that schizophrenia is associated with genetic variants and neurodevelopmental processes related to GABA and glutamatergic signaling (Howes and Shatalina 2022). Findings from Genome-Wide Association Studies (GWASs) have shown that genetic risk for schizophrenia affects both inhibitory, GABAB receptor components GABBR1 and GABBR2, as well as excitatory signaling proteins, such as NMDAR (subunit 2A) and the metabotropic glutamate receptor 3 (GRM3) genes, which may lead to disruptions in cortical E/I balance (Ikeda et al. 2019).

Recent Findings Related to Genetic and Schizophrenia

In recent years, scientific advances in the fields of single nucleotide polymorphisms (SNPs), copy number variations (CNVs), microdeletions, and epigenetic modifications have substantially contributed to our understanding of the genetic architecture of schizophrenia. Among these, SNPs—defined as single base pair alterations in the DNA sequence—have been widely investigated for their role in disease susceptibility. GWAS have identified numerous SNPs associated with schizophrenia, and when assessed using polygenic risk score (PRS) models, the cumulative effect of these variants has been shown to significantly contribute to individual disease risk (van der Merwe et al. 2019).

One of the most extensively studied SNPs in schizophrenia is rs1344706, located in the ZNF804A gene. Functional MRI studies have demonstrated that carriers of the risk allele exhibit impaired cognitive function and altered connectivity between the prefrontal cortex and hippocampus—regions critically involved in working memory and executive processing (Yang et al. 2021). Similarly, the brain-derived neurotrophic factor (BDNF) rs6265 (Val66Met) polymorphism, involving a methionine substitution in a neurotrophin essential for synaptic plasticity and learning, has been implicated in both elevated schizophrenia risk and increased vulnerability to cognitive dysfunction (Farcas et al. 2023). In addition, growing evidence points to the involvement of the immune system in schizophrenia pathophysiology. Notably, the rs2021722 SNP located in the human leukocyte antigen (HLA) region has been associated with heightened disease risk, particularly among individuals carrying the A allele (Li et al. 2021).

In addition, rare and large CNVs have been reported to occur more frequently in individuals with schizophrenia compared to the general population (Szecówka et al. 2023). In particular, microdeletions in the 22q11.2 region have been identified as one of the most well-established genetic risk factors for schizophrenia, and there is strong evidence that they are linked to impaired neurodevelopment and contribute significantly to disease pathogenesis (Karayiorgou et al. 2010). Beyond 22q11.2, additional recurrent microdeletions at 1q21.1, 15q13.3, and 16p11.2 have also been associated with increased schizophrenia susceptibility. These regions encompass genes that play essential roles in synaptic function, neuronal development, and intracellular signaling, which are all processes critical for the formation and maintenance of neural circuits underlying cognition and behavior. Therefore, it is thought that disruptions in these regions contribute to the emergence of the schizophrenia phenotype by leading to the disruption of basic neurobiological mechanisms (Rujescu, 2017).

In patients with schizophrenia, the role of epigenetic mechanisms, particularly DNA methylation and histone modifications, has become increasingly evident in recent years. Aberrant epigenetic regulation is thought to alter gene expression without modifying the underlying DNA sequence, thereby influencing neurodevelopmental and neurochemical pathways implicated in the disorder. Notably, increased DNA methylation of the REELIN and GAD1 genes has been observed in individuals with schizophrenia, which may contribute to disease pathophysiology by reducing the expression of these genes, both of which are critical for GABAergic neurotransmission and cortical development (Tavitian et al. 2025).

Discussion

Briefly, DA hypothesis is associated with D2R blockade and amphetamine-related psychosis in positive symptoms and respond to first generation antipsychotics. However, positive symptoms, negative symptoms and cognitive function is seen in second generation antipsychotics with poly neurotransmission affinity. Clozapine an antipsychotic drug is used for treatment-resistant schizophrenia (TRS) patients experiencing resistance to other medication. TRS patients showed decreased presynaptic DA synthesis in the striatum with clozapine therapy. This observation in TRS patients altered by antipsychotics is not explained by only the DA hypothesis. Furthermore, latest studies reported that schizophrenia is associated with glutamatergic mechanisms. Phencyclidine (PCP) and ketamine, N-methyl-d-aspartate (NMDA)-type glutamate receptor antagonists, induced positive and negative schizophrenia-like symptoms in healthy individuals (Huang et al. 2020). On the other hand, abundant DA release in presynaptic area to the classical DA hypothesis or postsynaptic increased density/sensivity of D2R causing schizophrenia-like symptoms

were later confirmed. However, overactivation of D2R does not assume that DA hyperactivity completely clarify the symptoms of schizophrenia (Kapur 2003). In conclusion, researchers modified the DA hypothesis to the new findings about schizophrenia molecular pathology. They concluded DA levels change with antipsychotic, TRS patients and some blockers of glutamate NMDA receptors might cause schizophrenia-like psychosis (Peleg-Raibstein and Feldon 2008).

No hypothesis has been developed solely based on neuromediators (DA or serotonin) to explain the underlying pathophysiology of schizophrenia. Numerous hypotheses have been produced based on neuroinflammation, cannabinoids, gut-brain axis model and oxidative stress for schizophrenia. In addition, genetic factors including single nucleotide polymorphisms, copy number variation, microdeletions and epigenetic changes have been revealed.

Current pharmacotherapies primarily rely on DA and serotonin receptor antagonists or partial agonists. However, novel agents such as lumateperone (which targets serotonin, DA, and glutamate pathways), pimavanserin (a selective 5-HT2A inverse agonist), roluperidone (targeting sigma-2 and 5-HT2A receptors), and mGluR2/3 agonists represent a promising shift toward mechanism-specific treatments. Furthermore, the adjunctive use of anti-inflammatory agents has shown potential in improving treatment outcomes, highlighting the need for transdiagnostic approaches that target shared molecular pathways (Ľupták et al. 2021).

Future studies should focus on elucidating the functional interplay between neurotransmitter systems and immune signaling pathways, leveraging systems biology and omics-based methods. Additionally, identifying reliable biomarkers that predict treatment response and stratify patients by molecular subtype remains an urgent clinical priority. Integrating longitudinal neuroimaging, genetic profiling, and clinical data could yield a precision psychiatry framework that redefines both diagnosis and therapeutic targeting.

Conclusion

Schizophrenia is now recognized as a multifactorial neuropsychiatric disorder involving complex interactions between genetic, environmental, neurodevelopmental, immune, and neurochemical factors. While dopaminergic dysfunction remains a cornerstone of our understanding, it is insufficient as a standalone explanation. Moving forward, comprehensive models that incorporate glutamatergic, GABAergic, serotonergic, and inflammatory mechanisms—along with genetic and epigenetic contributions—are essential for developing more effective and personalized treatments.

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