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The Biochemical Basis of Schizophrenia: The Dopamine Hypothesis and Beyond

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ABSTRACT

Schizophrenia is a complex neuropsychiatric disorder marked by a wide spectrum of symptoms, yet its biochemical basis remains unclear. While the classical dopamine hypothesis links excess dopaminergic activity to hallucinations and delusions, recent research implicates glutamatergic, GABAergic, serotonergic, and cholinergic systems, along with inflammatory and oxidative stress pathways. This paper argues that schizophrenia results from interactions among multiple neurotransmitter and receptor systems. By reviewing neuroimaging, pharmacological, and clinical trial evidence, it demonstrates that understanding receptor-specific contributions is crucial for developing targeted therapies addressing both cognitive deficits and affective symptoms.

Keywords: *Schizophrenia, Dopamine Hypothesis, Glutamate Dysfunction, NMDA Receptor Hypofunction, GABAergic Dysfunction, Serotonin Modulation, Neuroinflammation, Personalized Psychiatry*

INTRODUCTION

Affecting nearly 24 million people (or 1 in 300 people) worldwide, schizophrenia ranks among the top contributors of global disability, but it still remains a mystery to many of those who study it. (1) Its symptoms include but are not limited to persistent delusions and hallucinations, experiences of influence, control or passivity, disorganized thinking and behavior, negative symptoms like limited speech, restricted experience and expression, inability to express interest or pleasure, social withdrawal, and/or extreme agitation or slowing of movements.

People with schizophrenia often also experience persistent difficulties with their cognitive or thinking skills. At least one third of the people with schizophrenia experience complete remission of symptoms. Some people experience worsening and remission of symptoms periodically throughout their lives, others, a gradual worsening over time. (2)

The dopamine hypothesis is one of the oldest and most influential theories about the causes of schizophrenia. It suggests that the disorder is linked to an overactivity of dopamine, a brain chemical involved in thinking, emotion, and reward. Early versions of the theory focused only on too much dopamine in certain brain regions, but later versions recognised that imbalances—too much in some areas and too little in others—may both play a role. Over time, this hypothesis has expanded to include how stress, genetics, and drug use might all increase dopamine activity and contribute to the development of symptoms like hallucinations and delusions. (3)

While the dopamine hypothesis was originally supported by the effects of antipsychotic drugs, this assumes they reverse an underlying disease mechanism—an idea that remains unproven (4). In reality, the fact that antipsychotics alleviate symptoms by blocking dopamine D_2 receptors does not directly confirm that excess dopamine causes schizophrenia. These medications are effective mainly for the positive symptoms of schizophrenia, like hallucinations and delusions, but have limited impact on negative symptoms or cognitive deficits. Furthermore, they often take weeks to show clinical effects despite blocking dopamine receptors almost immediately—suggesting a more complex downstream mechanism at play. Stimulants can induce psychosis, but they affect multiple neurotransmitters, not just dopamine. Additionally, second-generation antipsychotics also act on serotonin receptors, yet they are still effective in treatment, pointing toward a more multifactorial neurochemical basis (5). Imaging and biochemical studies offer mixed or inconclusive findings, often without controlling for key variables like stress or prior medication. Simply put, the pharmacological effects of these drugs have provided correlational support, not causal proof, for the dopamine hypothesis. This has prompted investigations into other neurotransmitter systems, including glutamate, GABA, and serotonin, all of which appear to play critical roles in the broader neurobiology of schizophrenia. (6)

This paper aims to re-examine the dopamine hypothesis through the lens of new research, while also considering other neurochemical contributors to schizophrenia. It further explores integrative frameworks and future directions, with an emphasis on novel therapeutic strategies, advances in neuroimaging and biomarkers, and emerging insights into genetic vulnerability and other neurodevelopmental factors.

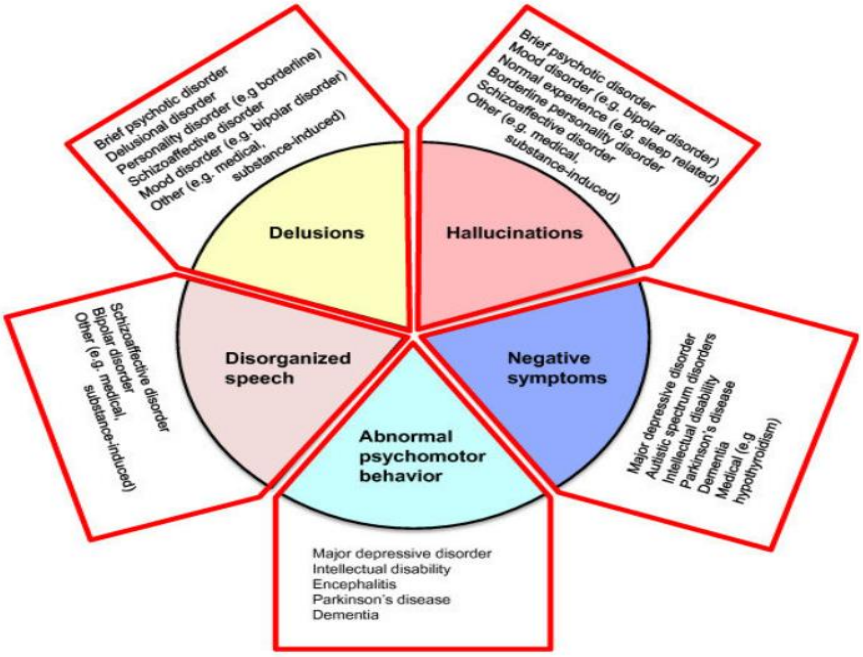

Figure 1 - Indicating the five main symptom domains in schizophrenia. For a diagnosis, these symptoms generally need to co-occur for one month or more. The figure shows how each of these symptom domain overlaps with other disorders.

1. THE DOPAMINE HYPOTHESIS - ORIGINS, REVISIONS, AND CURRENT EVIDENCE

1.1 Classical Framework and Foundational Evidence

The Dopamine Hypothesis of schizophrenia began with the surprising discovery in the 1950s that a drug called chlorpromazine could greatly reduce symptoms like delusions and hallucinations. Delay, Deniker and Harl reported this effect and started interest in finding a brain-chemical explanation for schizophrenia. (7) A few years later, Carlsson and Lindqvist found that chlorpromazine and another drug, haloperidol, increased the breakdown products of dopamine in the brain. This suggested that these drugs operated by blocking dopamine activity. (8)

In 1966, van Rossum proposed the first clear statement of the dopamine hypothesis, suggesting that schizophrenia might be caused by too much stimulation of dopamine receptors in the brain. (9) Support for this idea came from studies by Angrist and Gershon, who showed that taking high doses of amphetamines – which release dopamine – could cause symptoms very similar to schizophrenia. These symptoms went away after antipsychotic treatment. (10) Finally, Seeman and colleagues found that strength of antipsychotic drugs in treating schizophrenia matched how strongly they blocked dopamine D_2 receptors. This finding became one of the strongest pieces of evidence for the original version of the dopamine hypothesis. (11)

1.2 Limitations and Pharmacological Challenges

While traditional antipsychotic drugs that block dopamine D_2 receptors can help reduce schizophrenia symptoms, they also come with important drawbacks (12). One major issue is that around one-third of patients don't respond to these treatments, known as treatment-resistant schizophrenia. Some of these patients actually have normal dopamine synthesis levels, suggesting that dopamine might not be the main problem for them. (13)

Moreover, antipsychotics can cause serious long-term side effects. These include movement disorders like tardive dyskinesia and metabolic problems like weight gain and diabetes, which can significantly lower quality of life. (14) In rare cases, the brain may become overly sensitive to dopamine after long-term treatment (known as dopamine hypersensitivity), which can make symptoms worse if medication is stopped too quickly. (15)

Finally, because dopamine-blocking drugs mainly target 'positive' symptoms (like hallucinations), they're often less effective at improving negative symptoms (such as emotional withdrawal) and cognitive issues – this points to the need for treatments that go beyond the dopamine system. (16)

1.3 Modern Revisions – Dual-Pathways and Salience Models

There are four major dopaminergic pathways in our brain – mesolimbic, mesocortical, nigrostriatal and tuberoinfundibular. In more recent years, researchers have updated the dopamine hypothesis by emphasizing that schizophrenia symptoms may result from imbalanced dopamine activity across two of these pathways – the mesolimbic and the mesocortical. The mesolimbic pathway projects from the ventral tegmental area (VTA) to the nucleus accumbens and amygdala. Heightened dopamine transmission along this circuit has been strongly linked to positive symptoms such as hallucinations, delusions, and thought disorder (17). This hyperactivity is thought to distort salience attribution, leading individuals to assign undue importance to irrelevant stimuli (18).

Meanwhile, the mesocortical pathway, which extends from the VTA to the prefrontal cortex, is associated with cognition, planning, and executive control. In schizophrenia, reduced dopamine activity in this circuit has been correlated with negative symptoms (e.g., anhedonia, social withdrawal) and cognitive impairments (e.g., working memory deficits, poor decision-making) (19). This hypofunction may explain why many patients struggle with motivation and higher-order thought processes, even when positive symptoms are managed through antipsychotic treatment (20).

Another key idea is the distorted salience model. Scientists now believe that excess, random bursts of dopamine might make the brain "flag" unimportant things as if they were extremely significant.
That misplaced importance can push someone to form delusions or hallucinate, because their brain assigns meaning where there is none. (21) This model links brain-level dopamine dysfunction with real-world psychological symptoms.
The theory also includes a more dynamic, computational element: problems with how the brain processes prediction errors (like, mistakes in expectations). When dopamine signals go random, the brain misjudges what matters, reinforcing false beliefs (22).
Altogether, these modern models give a more complete picture of schizophrenia - not just dopamine alone, but how it's used differently across brain systems and thought processes.

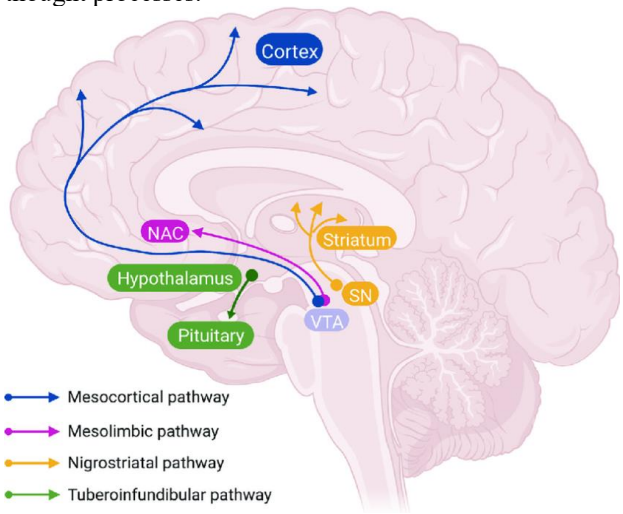

Figure 2 - Dopaminergic pathways in the brain. Dopaminergic pathways in the brain include the mesocortical pathway (blue) from dopaminergic neurons in ventral tegmental area (VTA) to cortex, the mesolimbic pathway (red) from VTA to nucleus accumbens, the nigrostriatal pathway (yellow) from substantia nigra to the striatum, and the tuberoinfundibular pathway (green) from hypothalamic nuclei (arcuate nucleus and periventricular nucleus) to the pituitary.

2. NEUROLOGICAL SYSTEMS BEYOND DOPAMINE

2.1 Glutamate Dysfunction and NMDA Receptor Hypofunction

While dopamine has historically dominated schizophrenia research, growing evidence suggests that glutamatergic dysfunction plays a central role in the disorder. In particular, abnormalities in the N-methyl-D-aspartate receptor, a subtype of glutamate receptor have been strongly implicated. NMDA receptor antagonists such as phencyclidine (PCP) and ketamine can induce schizophrenia-like symptoms, including both positive (hallucinations, delusions) and negative (social-withdrawal, anhedonia) symptoms, as well as cognitive impairments, in healthy individuals (23). This observation has led to the NMDA receptor hypofunction hypothesis, which posits that reduced glutamatergic signaling may underlie core features of schizophrenia (24).
Postmortem and neuroimaging studies have provided support for this theory, showing alterations in glutamate concentrations and NMDA receptor subunits in patients with schizophrenia (25). Hypofunction of NMDA receptors on inhibitory GABAergic interneurons may lead to cortical disinhibition, resulting in excessive downstream dopamine release in the mesolimbic pathway, thereby linking glutamate abnormalities to the classical dopamine hypothesis (26). Moreover, glutamate dysregulation may help explain why cognitive symptoms, which are poorly addressed by dopamine-targeting antipsychotics, remain a major challenge in treatment (27).

2.2 GABA and Serotonin: Inhibitory Dysfunction and Hallucinogenic Modulation

Apart from dopamine and glutamate, problems in the brain's GABA (check if we've and serotonin systems are also linked to schizophrenia. GABA is the brain's main inhibitory neurotransmitter, which means it helps "calm down" overactive brain circuits. In schizophrenia, research has found that certain GABA-producing neurons (especially those called parvalbumin interneurons) do not work properly. This reduces the brain's ability to keep activity balanced, leading to problems with thinking and memory (28). Studies on patients' brains after death also show lower levels of an enzyme called GAD67, which is needed to make GABA, suggesting that less GABA is available in schizophrenia (29). When GABA levels are too low, the brain becomes more excitable, which can worsen dopamine and glutamate abnormalities (30).
Serotonin, another key neurotransmitter, is mainly linked to mood and perception. The 5-HT2A serotonin receptor has drawn attention because drugs like LSD and psilocybin (hallucinogens) activate it, causing altered perceptions and hallucinations (31). Interestingly, some modern antipsychotic medications, such as clozapine, block this receptor, which helps reduce psychotic symptoms (32). This shows that serotonin is not just about mood but also directly involved in hallucinations and thought disturbances. In fact, activating serotonin receptors can also increase dopamine release in certain brain regions, which may explain why both systems are connected in schizophrenia (33).
Together, low GABA activity and abnormal serotonin signaling can disrupt the balance of brain circuits. This makes the brain more likely to experience hallucinations, confusion, and the distorted reality often seen in schizophrenia.

2.3 Immune and Oxidative Stress Pathways

In addition to neurotransmitter theories, researchers have found that schizophrenia is also linked to problems in the body's immune system. Many patients show higher levels of inflammatory markers, such as cytokines, which are chemicals released when the immune system is activated (34).

If these molecules remain elevated for long periods, they can interfere with how neurotransmitters like dopamine and glutamate work, and even damage important brain support cells (35). This kind of chronic inflammation may partly explain the memory, attention, and emotional regulation problems that are often seen in schizophrenia.

Closely connected to this immune dysfunction is oxidative stress, a condition where the brain experiences an imbalance between free radicals (harmful oxygen-containing molecules) and antioxidants, which normally protect against them (36). When oxidative stress becomes excessive, it damages brain cell membranes, proteins, and even DNA, reducing overall neural health.

Importantly, inflammation and oxidative stress can worsen each other in a cycle: inflammation raises free radical production, while oxidative stress further drives inflammation (37). Because of this, scientists are investigating whether treatments that reduce inflammation or boost antioxidants could help improve outcomes for patients alongside standard antipsychotic medications (38).

3. INTEGRATIVE FRAMEWORKS AND FUTURE DIRECTIONS

3.1 Genetic Vulnerability and Neurodevelopmental Factors

Schizophrenia is now understood as the result of both genetic risk and neurodevelopmental problems working simultaneously. Studies show that no single gene causes schizophrenia; instead, many small genetic variations combine to increase vulnerability (39). These variations often affect how brain cells communicate, especially through systems linked to glutamate and calcium channels (40). But genes alone are not enough. Early brain development factors – such as maternal infection during pregnancy, birth complications, or exposure to stress – can disturb how the brain matures, making someone with genetic risk more likely to develop the disorder (41).

Recent research also shows how genes and environment interact. For example, people with certain dopamine-related genetic variants are more vulnerable if they use cannabis or grow up in high-stress urban environments (44). Epigenetic changes, which have the ability to activate and deactivate genes, may further link stress and environment to brain changes (45). Looking ahead, scientists hope that combining genetic, imaging and biological markers will make it possible to predict risk early and intervene before full symptoms appear (46).

3.2 Neuroimaging and Biomarker Advances

Advances in Neuroimaging have provided critical insights into the biological basis of schizophrenia. Large-scale MRI studies consistently report reductions in grey matter volume, particularly in the prefrontal cortex and hippocampus, which are regions crucial for decision-making, memory and emotional regulation (47). Functional MRI studies further show abnormal connectivity patterns across brain networks, supporting the idea that schizophrenia is best understood as a disorder of disrupted neural communication rather than isolated structural damage (48).

Alongside imaging, researchers are increasingly investigating biomarkers, objective biological signals that could improve diagnosis and treatment prediction. These include changes in inflammatory protein levels, neurotransmitter irregularities, and electrophysiological measures such as reduced P300 amplitudes, which are often observed in patients with schizophrenia (49). Integrating such biomarkers with neuroimaging and genetic findings offers a more complete view of the disorder's complexity, highlighting its multi-level nature from genes to brain circuits (50).

Looking ahead, combining genetic, imaging and biomarker data may help realize the promise of personalized medicine in schizophrenia. Early studies suggest that network-level brain changes and molecular markers could eventually guide individualized treatment strategies, enabling earlier intervention and better prediction of therapeutic outcomes (51). While challenges remain in clinical translation, these advances point toward a future where biological data play a central role in diagnosis management.

3.3 Novel Therapeutics and Personalized Psychiatry

Recent years have witnessed the development of new treatments for schizophrenia that go beyond the traditional dopamine – D2 receptor approach. Drugs targeting muscarinic acetylcholine receptors, particularly the M1 and M4 subtypes, have shown promise. For example, KarXT (a combination of xanomeline, an M1/M4 receptor agonist, and trospium) targets these receptors to improve both positive and negative symptoms, as well as cognitive deficits, which are often resistant to traditional antipsychotics (52),(53).. Another example is iclepertin (BI 425809), a glycine transporter-1 inhibitor, which in phase II trials showed improvement in cognition over placebo, offering hope for addressing the cognitive impairments that are hard to treat with standard antipsychotics (54).

Personalized psychiatry means tailoring treatment to each individual's biology and symptoms. This includes using biomarkers (such as genetics, neuroimaging, or EEG) to predict which novel drug a person might respond to best (55). It also involves monitoring side-effect risk (as there are trade-offs even among novel agents) and choosing therapies that balance efficacy and safety for that specific person. In the future, combining new pharmacological talents (TAAR1 agonists, glutamate modulators, etc.) with personalized diagnostic tools could lead to more precise and effective treatments (56).

CONCLUSION

Schizophrenia is one of the most complex mental disorders, and it cannot be linked to a single cause. The dopamine hypothesis has been the most widely accepted explanation, as it connects overactive dopamine activity to the symptoms of schizophrenia. However, modern research shows that other neurotransmitters like glutamate and serotonin are also involved. This indicates that schizophrenia should be seen as the result of several biochemical factors, rather than only one.

The findings of this research highlight the need for a broader approach that looks beyond dopamine and considers the combined influence of different biochemical pathways. Such a perspective is essential for improving both our scientific understanding and the treatment of schizophrenia.

Overall, while the dopamine hypothesis remains important, it is only part of the explanation. A key question for future studies is whether early detection of these biochemical changes could help prevent or reduce the severity of schizophrenia.

If scientists can identify these changes before symptoms fully appear, it could open the door to earlier interventions, potentially improving outcomes and quality of life for those at risk.

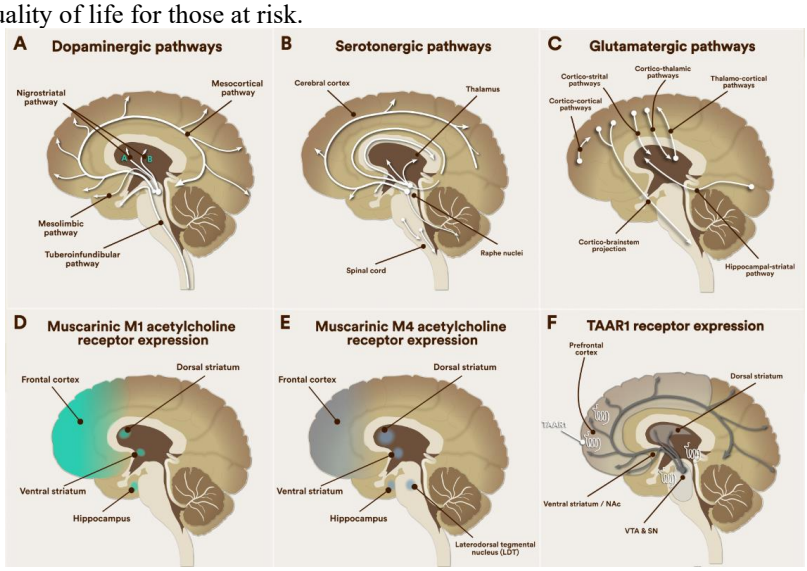

Figure 3 - Schematic representation of key neurotransmitter pathways and receptor distributions in the human brain relevant to schizophrenia: dopaminergic, serotonergic, and glutamatergic pathways, along with M1, M4, and TAAR1 receptor expression.

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