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The Neurobiological Basis of Schizophrenia: An Integrative Review

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Abstract

Background: Schizophrenia is a severe psychiatric disorder characterized by a complex, multifactorial origin. While dopaminergic theories have been predominant, contemporary perspectives highlight an integrated dysfunction across genetic, molecular, and neural circuit levels, rooted in neurodevelopmental abnormalities.
Objectives: This review synthesizes recent evidence from genetics, neuroimaging, and molecular psychiatry to present an updated model of schizophrenia pathophysiology. It focuses on the interplay between synaptic pruning, interneuron dysfunction, and brain network dysconnectivity.
Methods: We conducted a narrative, integrative review. Searches in PubMed, Scopus, and Web of Science (2014-2025) utilized terms like "schizophrenia neurobiology," "dysconnectivity," "NMDA receptor hypofunction," "parvalbumin interneurons," and "genetic risk." Evidence was thematically synthesized to construct a coherent pathophysiological model.
Results: Findings outline a pathway from genetic risk (e.g., complement C4 loci) to excessive adolescent synaptic pruning, leading to impairment of parvalbumin-positive GABAergic interneurons. This results in N-methyl-D-aspartate receptor (NMDAR) hypofunction, a disrupted cortical excitation/inhibition balance, and aberrant neural oscillations. These local deficits manifest as large-scale dysconnectivity within cortico-striato-thalamo-cortical (CSTC) circuits, underpinning positive, negative, and cognitive symptoms. Dopaminergic dysregulation is positioned downstream of primary glutamatergic/GABAergic pathology.
Conclusion: Schizophrenia is best conceptualized as a neurodevelopmental disorder of synaptic connectivity. Future therapeutics should target earlier pathological stages, such as immune-mediated pruning and glutamatergic signalling, offering potential for novel treatments and preventative strategies.

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Introduction

Schizophrenia remains one of psychiatry's most debilitating and complex disorders, impacting approximately 1% of the global population with severe consequences for individuals, families, and public health systems [1]. Its heterogeneous clinical presentation includes positive symptoms (e.g., hallucinations, delusions), negative symptoms (e.g., avolition, social withdrawal), and pervasive cognitive deficits [2]. As Jablensky [3] notes, it remains a syndrome defined clinically rather than aetiologically, reflecting its underlying biological complexity.

The limited efficacy and adverse effects of current dopamine D2 receptor-targeting antipsychotics underscore the insufficiency of monoamine-centric models to fully explain the disorder's pathogenesis [4]. These treatments offer minimal relief for negative and cognitive symptoms, which are key predictors of long-term disability [5]. This therapeutic impasse has driven a paradigm shift toward a multilevel, integrative understanding. The contemporary view frames schizophrenia not as a singular neurotransmitter disorder but as a neurodevelopmental syndrome of synaptic and circuit-level dysconnectivity[6].

This review synthesizes convergent evidence from psychiatric genetics, molecular neuroscience, and neuroimaging from the past decade. We trace the pathophysiological cascade from genetic and environmental risk factors to aberrant adolescent maturation, culminating in large-scale brain network disruption. By integrating findings on synaptic pruning, GABAergic interneuron vulnerability, NMDAR hypofunction, and dopaminergic dysregulation, we construct an updated narrative. This model explains diverse symptom profiles and highlights novel targets for prevention and mechanism-based therapeutics.

Methods

We employed a narrative synthesis methodology. A systematic search was conducted in PubMed, Scopus, and Web of Science for English-language articles published between January 2014 and March 2025. Key search terms included: "schizophrenia AND (neurobiology OR pathophysiology)", "genetics AND schizophrenia", "neuroimaging AND schizophrenia", "dysconnectivity", "NMDA receptor hypofunction", "GABA interneurons", "parvalbumin", "synaptic pruning", and "cortico-striato-thalamo-cortical circuits". The focus was on human studies, meta-analyses, and seminal animal models. Retrieved evidence was organized thematically into Genetics, Neurochemistry, Neurodevelopment/Neuroanatomy, and Neural Circuits to construct a logically coherent, evidence-based narrative.

Results & Discussion

Genetic Architecture and Neurodevelopmental Origins

Large-scale genomic studies confirm a polygenic architecture for schizophrenia, involving common variants of small effect and rare, high-penetrance copy-number variants (CNVs) [7]. Notably, genes implicated are enriched in pathways critical for synaptic function and neurodevelopment [8, 9]. A landmark finding involves the complement component 4 (*C4*) locus, where specific alleles increase *C4A* expression, potentially driving excessive complement-mediated synaptic pruning during adolescence—a critical period for disease onset [10]. This supports a neurodevelopmental "two-hit" model, where genetic vulnerability interacts with environmental stressors (e.g., obstetric complications) [14], leading to aberrant synaptic refinement.

From Synaptic Pathology to Circuit Dysfunction

The revised model positions dopaminergic dysregulation as secondary to upstream pathology. Central is the glutamate hypothesis of NMDAR hypofunction[16]. NMDAR hypofunction preferentially affects parvalbumin-positive (PV+) GABAergic interneurons, which are vital for generating gamma oscillations and neural synchrony [18]. Their impairment leads to a cortical excitation/inhibition (E/I) imbalance, disrupting cognitive coordination and perception [19]. This is evidenced by postmortem findings of reduced GABA-synthesizing enzyme GAD67 in the prefrontal cortex [20].

This interneuron vulnerability is exacerbated by aberrant adolescent synaptic pruning, potentially amplified by *C4* risk alleles and neuroinflammation [24, 25]. The resultant excessive synaptic loss contributes to the grey matter reductions observed in neuroimaging studies [23]. Structurally, diffusion tensor imaging reveals white matter integrity reductions [26]. Functionally, fMRI shows dysconnectivity within large-scale networks: hyperconnectivity in the Default Mode Network is linked to hallucinations, while hypoconnectivity in the Frontoparietal Network underlies cognitive deficits [27, 28].

Integrated Neural Circuit Model

Symptoms map onto specific dysfunctional circuits:

Positive symptoms are linked to mesolimbic dopamine pathway hyperactivity, likely downstream of hippocampal and cortical dysregulation [29].

Negative and cognitive symptoms are associated with mesocortical dopamine hypoactivity and reduced hippocampal-prefrontal connectivity [30, 31].

Dysfunction in Cortico-Striato-Thalamo-Cortical (CSTC) loops is critical for gating information and coordinating thought, linking circuit disruption directly to core symptomatology [32].

Clinical Implications

This integrative model has significant translational implications. While D2 antagonists remain first-line for acute psychosis, future therapeutics should target earlier pathological nodes:

Glutamatergic agents (e.g., mGluR2/3 modulators) to restore NMDAR signalling tone [36].

GABAergic strategies to enhance interneuron function and gamma oscillations [37].

Immunomodulation (e.g., minocycline) to temper neuroinflammation and synaptic loss [38].

Circuit-based neuromodulation (e.g., rTMS to the dorsolateral PFC) to normalize network activity [39].

Critically, the neurodevelopmental perspective highlights a preventive intervention window in clinically high-risk individuals, using biomarkers for early psychosocial or pharmacological strategies [40]. Future research must adopt longitudinal, translational designs integrating multi-omics data with multimodal neuroimaging [45]. Embracing frameworks like the Research Domain Criteria (RDoC) may help deconstruct syndromal heterogeneity into biologically grounded subtypes, paving the way for personalized medicine in psychiatry [48].

Conclusion

The neurobiological understanding of schizophrenia has evolved from a single-transmitter model to a sophisticated framework of developmental dysconnectivity. This review synthesizes a cascade from genetic risk to excessive pruning, interneuron impairment, E/I imbalance, and large-scale network disruption. While challenges remain, this integrated view moves the field beyond symptomatic dopamine blockade toward mechanism-based interventions, offering hope for altering the disease trajectory and improving outcomes for individuals with schizophrenia.

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Authors Contributions

The authors contributed to the data analysis. Drafting, revising and approving the article, responsible for all aspects of this work.

Conflict of Interest

None

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