Unravelling Schizophrenia: Genetic, Immune, Therapeutic, and Neurological Insights

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Schizophrenia is a complex psychological disorder that has long eluded a thorough understanding of disease causes and practical therapeutic approaches. This paper focuses on recent schizophrenia research findings and highlights the interconnections between the fields of genetics, immunology, neuroscience, and therapeutics. Additionally, this paper examines genomic research that indicates the polygenic origins of the illness, including copy number variants (CNVs) and risk alleles for genes involved in biological processes affecting schizophrenia, such as neuroinflammation. Immune system dysregulation, typified by increases in proinflammatory cytokines and c-reactive proteins, is highlighted as a contributor to schizophrenia pathogenesis. Deficits in brain structural integrity and neurotransmitter systems, which underlie schizophrenia symptoms such as delusions and hallucinations, are revealed by neuroimaging and post-mortem studies. In addition, this review paper highlights potential novel therapeutic avenues for schizophrenia patients. This analysis presents a comprehensive understanding of schizophrenia by integrating these distinct yet connected research areas, opening possibilities for improvements in patient outcomes, schizophrenia diagnosis, and treatment.

Keywords: Copy Number Variants, Schizophrenia pathology, Immune dysfunction, Synaptic pruning

Introduction

Schizophrenia is a severe psychological disorder that significantly affects an individual's cognitive, emotional, and behavioral processes. Schizophrenia is characterized by distortions in thought processes, perceptual experiences, emotional regulation, language use, sense of identity, and behavioral manifestations [1,2]. Typical symptoms of schizophrenia include five domains: delusions, hallucinations, disordered thinking and speech, grossly disordered or aberrant motor behavior, including catatonia, and negative symptoms, such as social withdrawal characterize schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). Schizophrenia is influenced by genetic predispositions, environmental influences, and alterations in brain chemistry and neuroanatomical structures [3,4].

In the context of schizophrenia, co-influential factors are factors that interact and collectively contribute to the onset and progression of schizophrenia. Together, these variables frequently interact in intricate ways to affect susceptibility to schizophrenia. Such co-influential factors include brain anatomical changes, immune and cellular abnormalities, and genetic components such as CNVs.

CNVs are genetic variations in the human genome caused by variations in the number of copies of a specific DNA region [5]. They are crucial for understanding disease relationships but can be difficult to analyze due to their complexity. Understanding the effects of CNVs can provide a new perspective on disease etiologies. Many CNVs involve genes essential for neurodevelopment and synapse function, highlighting the role of synaptic and neurodevelopmental pathways in schizophrenia's pathophysiology [6].

Additionally, schizophrenia is influenced by the inflammatory theory. The inflammatory theory focuses on molecular mechanisms and immune system changes, which have led to advancements in understanding the disease [7]. Advancements in technology, such as single nucleus RNA sequencing (snRNA-seq), have helped identify molecular causes and gene expression patterns [8,9]. This approach combines genomic approaches and studying pro-inflammatory cytokines, lymphocytes, and c-reactive proteins to advance in new treatment targets.

Schizophrenia is affected by neurotransmitter imbalances in the dopamine, serotonin, and glutamate signaling systems which can cause symptoms such as delusions, hallucinations, and mood changes [10]. Schizophrenia patients also exhibit grey matter volume reductions and white matter abnormalities, which can impair brain connectivity and functioning [11]. Neuroimaging techniques reveal structural abnormalities and functional dysconnectivity, potentially impacting inflammation, brain immunity, and brain homeostasis [12–14].

Schizophrenia has no known cause or cure, although advances in brain imaging, behavioural research, and genetics have allowed scientists to better understand neural mechanisms affecting schizophrenia and identify potential novel safe and

efficacious therapies[15]. Although current therapies have been efficacious in 50% of schizophrenia patients, there is a great need to identify the cause of Schizophrenia to provide more targeted, effective treatments for patients[16]. Comprehending the complex characteristics of schizophrenia is essential for creating effective interventions and improving our comprehension of treatments. This paper will look at how the complexity of schizophrenia is being unravelled by combining genetic, immune, neurological, and therapeutic approaches.

Therapies, Medication and Treatment-resistant Schizophrenia patients

Current therapeutics for schizophrenia target symptoms including hallucinations, delusions, disordered thinking, and decreased cognitive functioning. Antipsychotic drugs are the primary form of treatment for schizophrenia and are critical for symptom management and relapse prevention. First-generation and second-generation antipsychotics are the two primary categories into which these drugs are divided[17]. Although first-generation antipsychotics work well, serious adverse effects, such as extrapyramidal symptoms, are frequently associated with their use. The fewer adverse effects of second-generation antipsychotics, such as olanzapine and risperidone, make them the preferred medication even if they are implicated in metabolic problems like diabetes and weight gain[16]. There are many combinations of medications and therapies for schizophrenia patients, which all work incredibly diversely.

Current Medications and Therapies

Antipsychotic drugs continue to be the main form of treatment for schizophrenia, with the primary goal of reducing positive symptoms like delusions and hallucinations. New antipsychotic drugs including cariprazine are now available in the clinic; these drugs have improved side-effect profiles and efficacy compared to earlier generations of antipsychotics[18]. The introduction of an approved transdermal patch for treating adult schizophrenia marks a significant advancement in therapeutic strategies, offering improved patient comfort and adherence. This innovative delivery method employs asenapine, an atypical antipsychotic, and is under investigation for its potential to boost treatment compliance and maintain more consistent drug concentrations in the body compared to traditional oral administration[19].

Additionally, glutamatergic regulation has been identified as a potential treatment approach for schizophrenia, with promising but largely experimental results that are not yet firmly established[20]. Glutamatergic regulation encompasses the processes that govern the release, receptor binding, and reuptake of glutamate, the brain's principal excitatory neurotransmitter, to maintain optimal neural communication and function[21]. While these interventions show potential to enhance overall outcomes for patients, further research is needed to confirm their efficacy and safety. These therapies focus on the negative and cognitive aspects of schizophrenia, which are frequently more resistant to standard antipsychotic therapy. One major development in the treatment of schizophrenia is the creation of long-acting injectable (LAI) antipsychotic medicines. LAIs are specialized drug formulations designed for intramuscular or subcutaneous administration, engineered to gradually release the active therapeutic compound over an extended period, typically spanning several weeks to months[22]. By guaranteeing constant adherence to medications and lowering relapse rates, LAIs have been demonstrated to lower hospitalization rates, especially when started early in the development of schizophrenia[23].

Despite these developments, there are still complications, especially when meeting the comprehensive needs of schizophrenia patients. Many current treatments concentrate on the most common symptoms, frequently failing to address less common, co-occurring symptoms such as cognitive deficits. It is critical to find novel pathways involved in schizophrenia pathogenesis to create therapies that are more effective and tolerable for a wider range of symptoms[24].

Treatment-resistant Schizophrenia

One major obstacle to treating schizophrenia is treatment-resistant schizophrenia (TRS). About one-third of people with schizophrenia do not respond well to traditional antipsychotic drugs, which results in ongoing psychotic symptoms and decreased cognitive functioning[23]. The most successful pharmacological treatment for TRS is still clozapine, an atypical antipsychotic[25]. Its greater success in treating resistant positive symptoms is attributed to its unique action, which involves inhibition of serotonin 5-HT2A and dopamine D2 receptors[26]. However, clozapine does not work for a significant 50-60% percentage of individuals, which emphasizes the need for other therapeutic approaches[23]. In TRS, the effective use of combination therapies, which combine antipsychotics with other therapeutic agents, is currently being investigated. These strategies seek to address multiple symptom domains within schizophrenia to provide better results for those with complicated cases of schizophrenia or TRS.

Therapies targeting neurotransmitter systems affected in schizophrenia patients can be used in addition to current antidepressants, mood stabilizers, or glutamatergic drugs to improve therapeutic responses[15]. For example, the addition of the glutamate-release inhibitor lamotrigine has demonstrated benefits in decreasing depressive and cognitive symptoms in patients with TRS[27]. However, there is still little proof of efficacy for combination therapies, and it is important to carefully assess any possible drug interactions and negative effects of combination therapies prior to approving them for schizophrenia patient treatment[28].

Additionally, psychosocial approaches including cognitive behavioral therapy and family interventions have been suggested for schizophrenia[29]. These treatments have the potential to improve outcomes for TRS patients by assisting patients in creating coping mechanisms such as stress management and social skills training, increasing compliance with medications, and enhancing general daily functions[23,30]. In cases that are resistant to standard treatments, new therapies including electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) have demonstrated potential in reducing negative, positive and cognitive symptoms[31–33]. While ECT uses controlled seizures to create therapeutic benefits, TMS is a non-invasive brain stimulation therapy that modifies cortical activity[32].

Given the diversity and complexity of TRS, a customized, multifaceted strategy is necessary. Patient response to various interventions may be influenced by variables such as the age at which psychosis first appears, the period of time symptoms goes untreated, history of substance usage, and treatment adherence[15,23]. It is also critical to investigate new therapeutic targets and pharmacological medicines tailored to treat TRS. Recent findings point to the possibility that neuroinflammation, oxidative stress, and glutamate dysregulation are involved in the pathophysiology of TRS, opening new directions for investigation and possible therapeutic targets[34,35].

Genetic Implications in Schizophrenia

Considering the high heritability and intricate complexity of schizophrenia, which involves numerous genes and variants, genetics is essential to understanding schizophrenia. Researching genetics can help develop more effective preventative, therapeutic, and diagnostic measures. Geneticists use single-nuclei isolated from tissues to analyze the gene expression profiles using snRNA-seq. It is a modification of single-cell RNA sequencing, or scRNA-seq, and aids in the comprehension of the cellular composition of many tissues by researchers. These findings may contribute to the comprehension of the molecular origins of schizophrenia and help identify new targets for treatments in schizophrenia[8].

Copy Number Variants

A type of structural variation in the human genome known as a CNV is caused by variations in the number of copies of a specific DNA region. Although CNVs are important for understanding the relationships between diseases, their analysis is difficult because of their complexity inside repetitive DNA sequences. In order to fully understand the impact of copy number variations and their potential to disrupt multiple genes simultaneously, researchers must navigate the complex landscape created by the variability in CNV size, which can range from small deletions or duplications to large chromosomal abnormalities[36]. Significant disruptions in gene function in the context of schizophrenia can be caused by CNVs, mostly through dosage effects, in which the number of copies of a gene changes and affects the production of proteins. These alterations may have an impact on neuronal growth, synapse function, and the neurotransmitter systems that are essential for processing emotions and cognition[37].

Many types of structural variants consist of new insertions, consecutive duplications, translocations, inversions, and deletions. CNVs can also be inherited or result from spontaneous de novo mutations. Copy number variation is categorized into two forms known as CNVs and copy number polymorphisms (CNPs). Larger structural changes in the genome are known as copy number variations, whereas variations that are more prevalent in the population are known as CNPs. CNPs are often shorter than 10 kilobases and frequently include genes linked to immunity. Some CNPs have varying copy measurements and are linked to conditions such as glomerulonephritis, Crohn's disease, and psoriasis[38]. CNVs can alter the balance of neurotransmitter systems, including the glutamatergic, and dopaminergic systems, which are linked to schizophrenia. CNVs observed in schizophrenia patients provide a genetic explanation for the neurochemical imbalances involved in schizophrenia, offering possibilities by which these genetic variants may worsen the symptoms of schizophrenia[39,40]. Many variants such as 22q11.2 and 2p16.3 deletions have been identified as leading causes of the pathogenesis of many genetically rooted diseases thus, understanding their effects can also provide a new outlook on the etiologies of diseases[41]. The understanding of the fundamental processes and possible treatment targets of schizophrenia has also been aided by genetic models that manipulate risk genes linked to schizophrenia, such as DISC1, NRG1, and dysbindin[42,43]. The intense involvement of CNVs in the pathogenesis of schizophrenia highlights the role that synaptic and neurodevelopmental pathways play in the pathophysiology of schizophrenia, which is consistent with the schizophrenia's onset in late adolescence or early adulthood, which is a crucial time for brain development[6].

The identification of certain CNVs is critical to improving schizophrenia diagnosis, prognosis, and treatment approaches. CNVs impact the genetic basis of the illness, contributing to the creation of a thorough understanding necessary for customized treatment strategies[44]. Furthermore, by analyzing protein in patient cell lines, CNVs have been connected to putative therapeutic targets, opening up new therapy options. Furthermore, the association between CNVs and disorders such as polycystic ovarian syndrome (PCOS) highlights the protective effects of medications like metformin against schizophrenia, emphasizing the role of genetic insights in identifying novel therapeutic targets[45].

Gene C4A & Synaptic Pruning

The intricate biological process method of forming a synapse through which neuronal information is transmitted is referred to as synaptogenesis[46]. Synaptogenesis is crucial in neuronal development to establish vital functions such as learning and memory. Accompanying this production of new synapses is synaptic pruning, which is a necessary and prompt process period of time that eliminates connections the brain no longer needs. Synaptic pruning is a naturally occurring process that begins to take place in early infancy and peaks during adolescence to remove redundant synaptic connections[47,48]. At the forefront of this synaptic pruning process are microglial cells that reside in the central nervous system and serve as the main components of the Central Nervous System's (CNS) innate immune system[49]. Although they make up less than 10% of all brain cells, microglia react robustly to brain infections. Excessive or prolonged microglial activation may be responsible for neuronal degeneration. It has recently been discovered that microglial activation has a close connection to the neurological pathology of schizophrenia in numerous locations of the brain[50]. (Figure 1)

The brain's process of synaptic pruning is greatly facilitated by the C4 gene, and especially by the protein C4A isoform. In humans, higher expression of C4A has been associated with a higher risk of schizophrenia. Genes C4A and C4B are located on the Major Histocompatibility Complex (MHC) class III. On human chromosome 6, the MHC is a genetic locus that plays a key role in immunity. The MHC is a set of genes that produce proteins on cell surfaces which help the immune system to detect foreign pathogens. Since the MHC locus spans several genes and is highly polymorphic, its relationship with schizophrenia is complex and difficult to understand. Although the exact mechanism behind the link between schizophrenia and the MHC locus remains unclear, new studies have linked different complement component 4 (C4) gene variants to the disorder[51].

Human C4A overexpression in B6 strain mice results in decreased cortical synapse density, increased synaptic pruning by microglia, and changed behaviour. This implies that abnormal brain circuits and behaviour in mice may result from excessive C4A-mediated synaptic pruning. The study on the mouse model emphasizes how C4A affects synaptic pruning and how it may be involved in disorders like schizophrenia[52]. Yilmaz et al. showed that mice overexpressing human C4A experienced reduced cortical synapse density, increased synaptic pruning, and behavioural alterations resembling those of schizophrenia. This work supports the importance of complement-mediated synaptic pruning in schizophrenia pathology by directly relating elevated C4A expression to abnormal synaptic elimination and phenotypes associated with schizophrenia[52]. Containing many distinct plasma proteins, the complement system reacts with pathogens by binding to them and triggers inflammatory responses to combat infection[53]. Complement C4 is a crucial component of the classical complement pathways and is necessary for innate protection against invasive microorganisms.

Microglia also play a significant role in synaptic pruning and release several chemokines, cytokines, and complement factors like C3, which regulate neuron-microglia communication. Complement C4 proteins promote the activation of C3 proteins involved in synaptic engulfment. The overexpression of gene C4 can result in excessive synaptic pruning. Mice that overexpress human C4A also exhibit larger quantities of C3 at neuronal synapses, suggesting C4A overexpression can result in excessive synaptic pruning[52]. This recognition of C3 by C4A and downstream complement pathway activation triggers the microglia to engulf and destroy the synapses. Through its capacity to bind synaptic proteins and initiate the conventional complement cascade, C4A marks synapses for phagocytosis by causing C3b deposition, which is recognized by microglial complement receptor 3 (CR3)[54–56]. Complement component C3 cleaves to produce C3b, an opsonin that forms convertases to enhance the complement response. C3b's interaction with phagocytic cells on complement receptor 3 makes it easier to remove tagged particles and is essential for synaptic pruning during brain development[57,58]. Microglia can prune synapses too much or too little, which can result in aberrant neural network formation and poor synaptic growth to contribute to the cognitive, sensory, and motor deficiencies associated with neurodevelopmental disorders.

Neurodevelopmental disorders such as schizophrenia and autism spectrum conditions are increasingly associated with disruptions to the normal synaptic pruning process carried out by microglia. Individual differences in C4A expression are mostly explained by genetic variation at the C4 locus, where larger copy numbers of the C4A gene often translate into higher amounts of C4A protein in the brain[51]. Strong correlations have been shown between the variability in C4A expression caused by structural variations in the C4 gene and the likelihood of getting schizophrenia. A higher expression of C4A is linked to a higher risk of acquiring schizophrenia[51,59]. Synaptic pruning disruptions can contribute to the etiology of autism spectrum conditions and schizophrenia by genetic and environmental variables that interfere with normal microglial activity during critical developmental phases[58].

CNV 22q11.2 Deletion Syndrome

Numerous studies have examined the impact of the CNV 22q11.2 gene in schizophrenia, suggesting its role in neuropsychiatric disorders. A particular kind of CNV known as deletions occurs when a chromosomal segment is absent. Deletions may lead to the loss of genetic material and depending on the genes impacted and the extent of the deletion, deletions may have varying effects. Deletions that perturb gene function can result

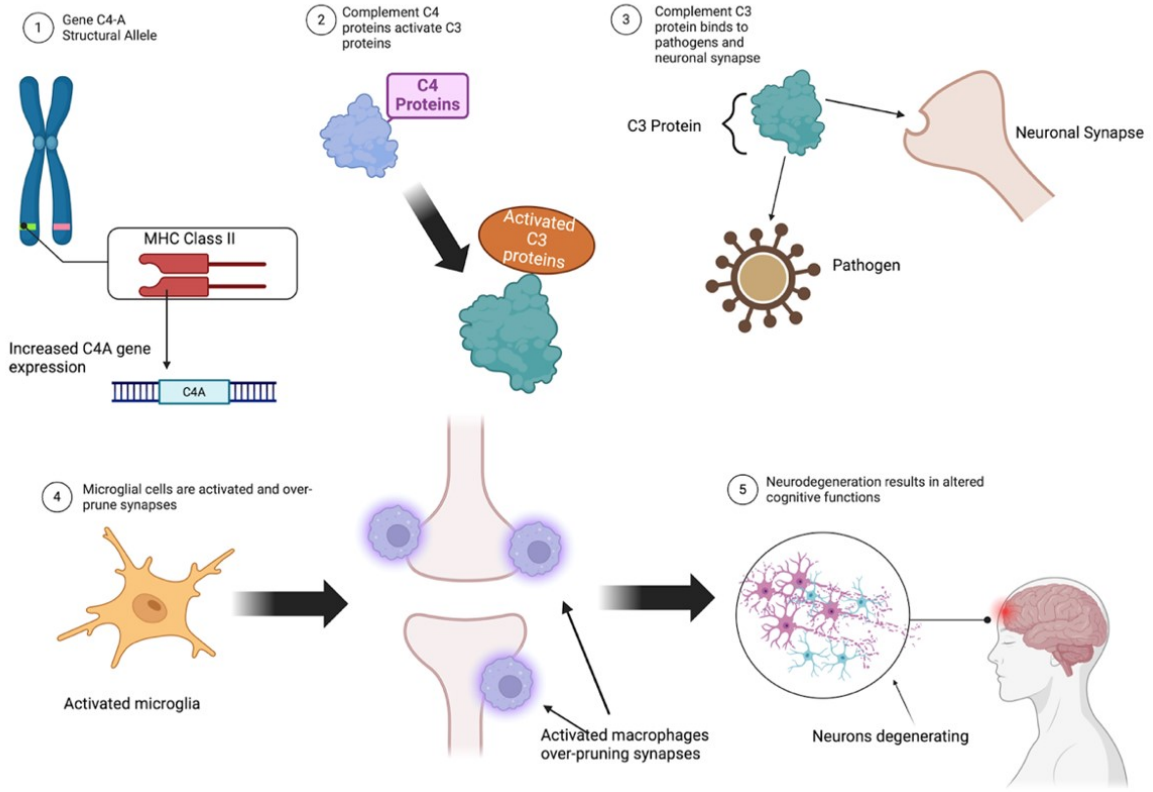

Fig. 1 Gene C4a and synaptic pruning — The potential process through which the C4A allele, found on the MHC locus, leads to synaptic pruning and neurodegeneration in schizophrenia is depicted in this figure. The C4A allele initially increases gene expression, which raises the amount of C4 proteins. C3 proteins are then activated by these C4 proteins. It has been shown that the extra C3 proteins bind to pathogens or, more importantly, neuronal synapses. The C3-tagged synapses stimulate the brain's primary immune cells, called microglial cells. The tagged synapses are engulfed and pruned by these activated microglia, a process that becomes excessive because of the excess C4A-driven C3 activation[52]. Reduced synaptic connections in neurons are displayed, suggesting a possible loss of neuronal connectivity and function involved in the pathogenesis of schizophrenia[51].

in genetic diseases. Gene expression and functionality may be impacted when a deletion lowers the number of copies of the gene, which may have an impact on phenotypic outcomes[60].

This particular deletion 22q11.2 is considered the strongest genetic risk factor for schizophrenia and affects approximately 25% of people with deletion syndromes (DS) which refers to a group of genetic disorders caused by the deletion of a chromosomal segment[61]. This highlights the importance of the 22q11.2 region in understanding the pathophysiology of schizophrenia and the possibility of developing new therapeutic strategies[62]. According to a noteworthy study by Forsyth et al., the CNV 22q11.2 gene loci area affects synaptic and gene regulatory pathways in both autism and schizophrenia[63]. Furthermore, recent studies have highlighted the relationship of the 22q11.2 deletion with different neural functions by identifying new genetic variations connected specifically to carriers of loss-of-function mutations with schizophrenia. This demonstrates how the gene affects how the disease expresses itself differently in each affected person[64].

The presence of 22q11.2 gene deletion has also been correlated to cognitive impairment. The majority of school-age children diagnosed with 22q11.2 DS have IQ values that are lower than average. With scores ranging from 70 to 75, the most prevalent cognitive characteristic is borderline intellectual ability. Along with difficulties with working memory, children with 22q11.2 deletions also showed difficulties with spatial perception and awareness. These findings suggest that attentional and operational cognition in 22q11.2 DS are caused by abnormalities in the parietal and frontal brain circuitry. Alongside cognitive deficits, anatomical abnormalities were common in children with 22q11.2 DS. The cortical thickness is similar overall, but in 22q11.2 DS, there is midline thinning in the cuneus, lingual gyrus, anterior cingulate, posterior cingulate gyrus, subgenual prefrontal, and occipital pole regions, and lateral thinning in the parieto-occipital, occipital pole, and inferior prefrontal regions; indicating brain areas involved in visual processing, regulation

of attention and emotion, episodic memory and crucial connection structures are most heavily affected by 22q11.2 DS. Functional relationships were observed between frontal/parietal diffusion tensor imaging (DTI) images measuring the callosal area and spatial attention, counting ability, math skills, and cognitive traits in 22q11.2 DS, indicating that interrupted connection may play a role in cognitive disabilities associated with 22q11.2 DS[65]. In addition, DTI uses measurements like mean diffusivity, which represents the overall diffusion magnitude, and fractional anisotropy to evaluate directional water diffusion, to quantify white matter microstructure. Important association tracts for social cognition and emotional processing, including the cingulum bundle, uncinate fasciculus, and inferior frontal-occipital fasciculus, are altered in 22q11.2 DS according to DTI studies[66,67]. DTI enables in vivo evaluation of the microstructure and integrity of white matter in individuals with schizophrenia. It is capable of picking up on minute white matter alterations that a conventional MRI could miss[68]. Given that 22q11.2 DS is strongly correlated with cognitive and anatomical abnormalities that are similar to those of schizophrenia patients, it is likely that gene 22q11.2 deletion plays a role in the pathophysiology of schizophrenia.

Given the increased likelihood of developing schizophrenia, those who have 22q11.2 DS may benefit from early intervention or treatment. Early markers of schizophrenia-like symptoms include hypocalcemia, agitation, and subthreshold psychiatric symptoms like anxiety. These markers should be monitored to help determine whether to start preventive measures[69,70]. Furthermore, the focus on early identification and intervention, along with the investigation of brain abnormalities and cognitive impairments by neuroimaging, underscores the possibility of creating innovative therapeutic strategies customized for this high-risk demographic[71].

NRXN1: The 2p16.3 locus

Schizophrenia and other neurodevelopmental disorders are strongly linked to the Neurexin 1(NRXN1) gene CNV at the 2p16.3 locus. NRXN1 is primarily involved in the establishment and upkeep of synapses by serving as a framework at the synaptic cleft[72]. Encoding neuronal cell adhesion molecules that affect synaptogenesis, synaptic structure, and function, the NRXN1 gene is essential for synaptic development and function. As a result, changes to NRXN1, such as deletions or duplications, may have a significant impact on brain circuits related to the pathogenesis of schizophrenia[73,74]. The NRXN1 gene, which is located on chromosome 2's short arm known as 2p16.3, has two main isoforms: NRXN1α and NRXN1β, which are produced by different promoters. With six laminin-neurexin-sex hormone-binding globulin (LNS) domains and three epidermal growth factor-like (EGF) sequences, the alpha isoform is substantially larger than its beta counterpart and allows for a wide range of interactions at the synaptic junctions[75]. LNS domains are protein modules that mediate interactions between proteins. These six domains enable the alpha neurexin isoform to participate in a variety of binding interactions whereas EGF sequences are another category of protein modules frequently involved in signaling and protein-protein interactions[57]. With the exception of the sixth LNS domain, the beta isoform lacks these domains and has a more specialized function in synapse maturation.

Given its many protein interaction domains and structural complexity, the alpha neurexin isoform can participate in a variety of chemical interactions that are essential for creating and preserving the complex synaptic connections between neurons. It is important to note that NRXN1 is expressed widely throughout the brain, highlighting its vital function in the central nervous system[76]. In order to create a trans-synaptic bridge that guarantees appropriate alignment and signalling between pre- and postsynaptic terminals, NRXN1 interacts with the neuroligins family of postsynaptic proteins to regulate excitatory and inhibitory synapses[77]. In addition to arranging the synapse architecturally, this interaction modifies the strength and flexibility of synapses, which are essential for memory, learning, and cognition. One of the main pathophysiological aspects of schizophrenia is synaptic dysfunction, which might result from these genetic changes interfering with the gene's normal function. The typical cognitive deficiencies associated with schizophrenia include problems in working memory, executive functioning, and social interactions and are consistent with the synaptic abnormalities linked to NRXN1 irregularities[78].

Abnormalities in immune cell function in schizophrenia patients

Schizophrenia is a multifaceted disorder characterized by many biological and environmental factors. The identification of multiple cellular components and aberrant processes linked with the pathophysiology of schizophrenia has led to a substantial advancement in understanding schizophrenia. The inflammatory theory of schizophrenia has been highlighted by studies exploring the role of immune cells in schizophrenia progression[7]. The inflammatory theory approach, which includes innovative genomic approaches with the investigation of pro-inflammatory cytokines and c-reactive proteins, opens the door to novel treatment targets and a more profound comprehension of the pathophysiology of schizophrenia.

Pro-inflammatory Cytokines

There is increasing evidence that inflammation plays a role in schizophrenia pathology, including the impact of immune system dysregulation early in life, genetic associations with immune-related loci, and elevated cytokine levels in patients[79–81]. Small signaling proteins called cytokines

are released by a variety of cells, including stromal cells, macrophages, microglia and lymphocytes. They are essential in controlling the maturation, growth, and responsiveness of immune cells as well as the immune response. Lymphocytes, monocytes, macrophages and microglia can all secrete proinflammatory cytokines, which can then act on other cell types to produce a variety of biological functions such as the activation of inflammatory reactions within the brain and in the periphery[82,83]. Research has demonstrated a strong correlation between the risk of schizophrenia and polymorphisms in genes encoding cytokines, including interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor-alpha (TNF-alpha). These findings suggest schizophrenia patients have a hereditary predisposition to immune dysregulation[84,85].

The majority of neuroinflammatory functions are carried out by activated microglia, which can release cytotoxic factors, including reactive oxygen/nitrogen species, excitotoxic glutamate, and proinflammatory cytokines. Cytotoxic factors are substances that have the direct ability to harm or kill cells, including neurons[86]. The release of pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, IFN- and chronic microglial activation have been suggested as probable processes underlying neurodegeneration observed in schizophrenia. Microglia can become primed by inflammation or infections, and their activation enables rapid immune responses to brain pathogens. However, if microglial activation states persist over an extended period of time, they can contribute to neurological conditions such as cognitive decline in schizophrenia[87]

Through controlling processes like cell division, migration, proliferation, and survival, the Wnt/β-catenin signalling pathway is an important cellular communication system involved in many physiological activities, including the production of proinflammatory cytokines. It is also critical for development and tissue homeostasis[88]. When this route is activated, β-catenin builds up inside the cell and moves to the nucleus, where it affects the expression of genes that control growth, division, and other essential functions. Studies have indicated that elevated expression of pro-inflammatory cytokines such IL-8, TNF-α, IL-1β, and monocyte chemoattractant protein-1 (MCP-1) can result from activation of the WNT/β-catenin pathway[89]. Several brain regions, such as the hippocampus, show abnormally high levels of essential proteins involved in this pathway, such as GSK-3β and β-catenin, among individuals with schizophrenia. Furthermore, dysfunctional Frizzled (FZD) receptors, which interact with WNT proteins, have been linked to schizophrenia. It is believed that these abnormalities in the WNT/β-catenin pathway play a role in the pathophysiology of schizophrenia[90–92]. (Figure 2)

About 40% of patients diagnosed with schizophrenia have been discovered to have higher levels of pro-inflammatory factors such as cytokines in their cerebrospinal fluid (CSF) and blood. Upregulated proinflammatory factors are indicative of inflammation of the central and peripheral nervous systems, which is linked to changes in cognition and neural anatomy[91]. Numerous cytokines such as IL-8, MCP-1, TNF-α, and IL-1β have been linked to the pathophysiology of schizophrenia and common abnormalities seen in patients. These cytokines influence brain development and mediate inflammatory processes. Experimental treatments on prenatal and perinatal rodents have been shown to cause behavioural abnormalities resembling schizophrenia after early-life exposure to these cytokines[?]. This provides credibility for the cytokine theory of schizophrenia etiology, which proposes that the disorder's reported behavioural and neurochemical abnormalities may be caused by inflammatory pathways mediated by cytokines.

The symptoms of schizophrenia may be exacerbated by abnormalities in the Wnt/β-catenin pathway, which can affect brain structure and function by interfering with neurodevelopment, synapse function, and dopaminergic system modulation. These disturbances may impact neuronal proliferation, migration, differentiation, and synaptic plasticity, which in turn may explain the complex symptomology of schizophrenia, including positive symptoms, negative symptoms, and cognitive deficiencies[91,93,94].

C-reactive Proteins

C-reactive protein (CRP) is an inflammatory factor produced by liver hepatocytes. CRP can act as an indicator for a number of inflammatory illnesses, such as infections, autoimmune diseases, and chronic inflammatory illnesses[95]. Elevated CRP levels have been correlated with cognitive deficiencies, symptom severity, and other clinical aspects of schizophrenia[96]. C-reactive protein (CRP) serves as a marker of inflammation and plays an important role in the innate immune response. There are two forms of CRPs: monomeric CRP (mCRP) and native pentameric CRP (nCRP). The plasma circulating form, known as nCRP, has the ability to permanently split into five mCRP monomers at sites of infection or inflammation. nCRP exhibits anti-inflammatory qualities by inducing phagocytosis, promoting apoptosis, and activating the classical complement system. Pro-inflammatory effects of mCRP include chemotaxis and recruitment of leukocytes to inflammatory areas, inhibition of apoptosis, and induction of pro-inflammatory cytokines such as MCP-1 and IL-8. IL-6 and TNF-alpha are generated by the body during the initial stage of inflammation to stimulate CRP expression[97]. CRP is a very sensitive indicator of inflammation as the liver produces it in response to inflammatory cytokines exponentially, typically within a few hours of the start of inflammation or infection[98].

CRP has been suggested as a contributing factor to the pathophysiology of schizophrenia symptoms. Orsolini's systematic review goes into greater detail about the importance of CRP and emphasizes how CRP levels are correlated with the severity of the illness, especially during the periods of worsening

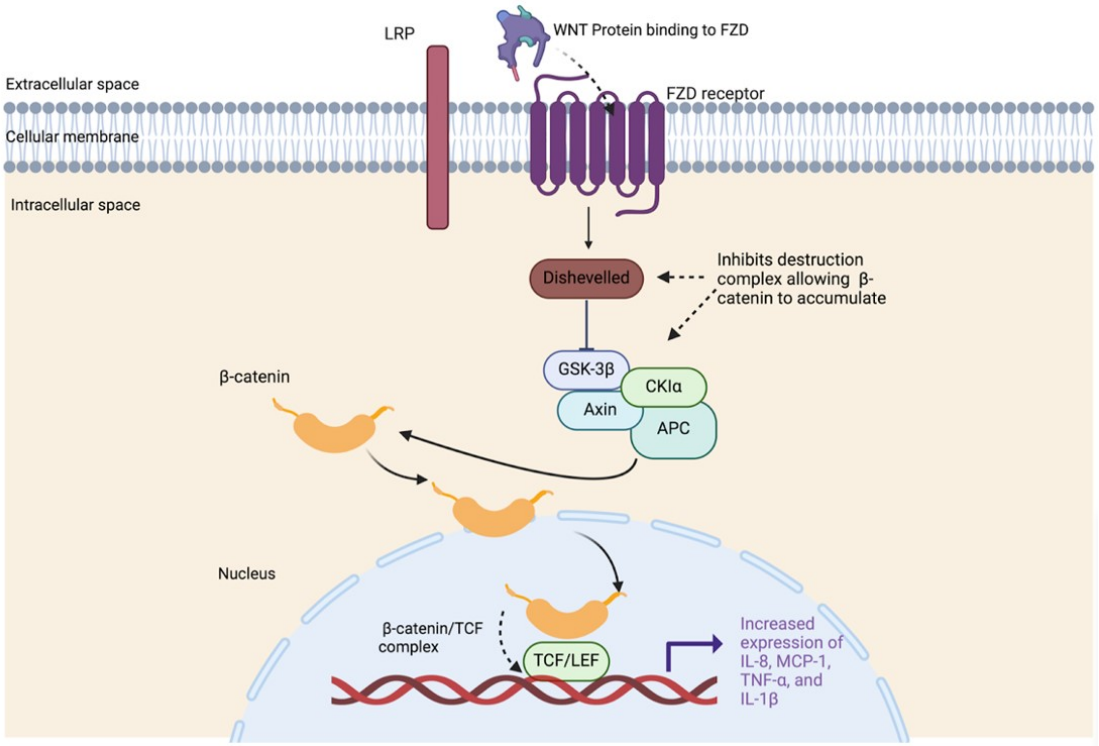

Fig. 2 WNT signaling pathway activation increases pro-inflammatory cytokine expression — The canonical WNT/β-catenin signalling pathway promotes the production of pro-inflammatory cytokines. The WNT protein binds the Frizzled receptor (FZD) to trigger the WNT/β-catenin signalling pathway. Dishevelled (DVL) is brought in because of this activation, disrupting the β-catenin destruction complex [88,93]. As a result, β-catenin builds up and moves into the nucleus, where it combines with TCF transcription factors to bind to different promoters depending on the specific genes being regulated and the biological context. Subsequently, the TCF/β-catenin complex increases the expression of cytokines that promote inflammation, including IL-8, MCP-1, TNF-α, and IL-1β. This process emphasizes how crucial WNT signalling is for controlling inflammation and how it may have consequences for inflammatory conditions like schizophrenia, where abnormal WNT pathway activity occurs [88,94].

symptoms. According to Orsolini's study, elevated CRP has also been linked to aggressiveness, negative symptoms, and catatonic features, suggesting that it may have wider effects on the clinical manifestations of schizophrenia [99]. In accordance with these results, increased CRP levels may reflect the underlying inflammatory processes that are involved in the pathophysiology of the condition. In addition, the correlation between CRP levels and schizophrenia severity highlights the critical role of inflammation and immunity in the pathophysiology of both schizophrenia and related aggressive behaviours [99]. The immune system may be activated in the pathway that connects CRP and schizophrenia; genetic and epidemiological research have linked infections, autoimmune diseases, and immue dysregulation to the development of schizophrenia [100]. Furthermore, the notion that CRP levels are consistently upregulated during severe psychotic episodes provides insight into the potential association of chronic inflammation with schizophrenia. The elevation of CRP was observed in 59.8% of schizophrenia patients during acute psychosis episodes and was correlated with more severe cortical neuropathology and cognitive deficits in patients [101]. The pathophysiological function of CRP in schizophrenia highlights an important connection between inflammatory processes and the behavioral, cognitive, and clinical aspects of the illness. These findings support the paradigm for inflammatory theories of schizophrenia. Connecting inflammation to schizophrenia symptoms may also provide innovative approaches to diagnosis and treatment that focus on reducing inflammation [96].

However, because there may be additional factors at play, interpreting CRP levels in the context of schizophrenia can be challenging. CRP levels can be independently raised by lifestyle decisions and co-existing medical disorders, such as obesity, smoking, and other physical ailments. This complicates the direct correlation between elevated CRP and schizophrenia [102]. For instance, smoking has been shown to trigger inflammatory reactions, and obesity has been associated with long-term low-grade inflammation. These factors may lead to elevated CRP levels, so it is important to evaluate inflammation markers carefully in patients with schizophrenia. The intricate relationship

between CRP levels and these confounding variables emphasizes the need for a thorough evaluation to identify the precise roles played by inflammatory processes in the pathophysiology of schizophrenia and the possible consequences for focused treatment approaches involving immune regulation [103].

Chemical and Structural Changes of the Brain

Neuroimaging

Brain anatomy abnormalities associated with schizophrenia such as expanded lateral and third ventricles, as well as decreased grey matter volumes in the prefrontal, superior temporal, and medial temporal regions have been identified using neuroimaging techniques such as magnetic resonance imaging (MRI) and functional MRI (fMRI). Patients' diminished grey matter volume and dilated ventricles on structural MRI scans indicate a continuing neurodegenerative process for schizophrenia patients. These results have implications for therapy, illness monitoring, and early identification of schizophrenia [12]. The integration of structural, functional, and molecular imaging techniques in multimodal neuroimaging approaches offer a more thorough comprehension of the neurological pathology of schizophrenia. However, it is important to recognize and carefully consider potential confounding factors, such as medication effects, the duration of illness, and comorbid disorders, when interpreting neuroimaging results in schizophrenia research. These variables can significantly impact brain structure and function, potentially concealing or altering the observed neuroimaging results.

The diminished functional connection between the thalamus and the prefrontal, temporal, and parietal cortices is known as thalamocortical dysconnectivity, and is consistently observed in patients with schizophrenia according to resting-state fMRI studies. Considering that thalamocortical dysconnectivity exists in all phases of schizophrenia, it is possible that this dysconnectivity is involved with positive and negative symptoms commonly observed in schizophrenia patients [13]. The severity of symptoms, including cognitive deficit, are correlated with the degree of dysconnectivity. Potential explanations of thalamocortical dysconnectivity include compromised synaptic plasticity and abnormalities in neurodevelopment. To fully understand this dysconnectivity and how it relates to the course of schizophrenia development and the treatment efficacy, longitudinal resting-state fMRI investigations are suggested. Giraldo-Chica et al. discovered that patients with schizophrenia perform worse cognitively due to decreased functional connectivity between the thalamus and cortices, which coordinate cortical activity and may contribute to higher cognitive difficulties associated with schizophrenia [104].

Grey Matter

The pathophysiology of schizophrenia is impacted by a reduction in grey matter volume, especially in vital brain areas such as the frontal cortex and cerebellum. This grey matter volume abnormality plays a role in both the onset and progression of schizophrenia, highlighting the connection between grey matter maintenance and schizophrenia [11].There is a complex connection between reduced grey matter volume and clinical results; patients with schizophrenia exhibit increased symptom levels as a result of decreased grey matter volume in particular brain locations such as the left hemisphere temporal regions such as the planum temporal and Heschl's gyrus which were associated with higher degrees of symptoms [82]. Positive symptoms are associated with lower grey matter volume in the middle and superior temporal lobe in early-onset schizophrenia patients [105].

Reduced grey matter volume in brain areas such as the prefrontal cortex, temporal lobe, and hippocampus is one of the major characteristics of grey matter abnormalities, which is a significant characteristic of schizophrenia [106]. As prefrontal grey matter is essential for working memory and decision-making, decreases in it may be a factor in cognitive abnormalities in schizophrenia [107]. According to longitudinal research, schizophrenia may cause more grey matter to be lost over time [11].

Neuroimaging studies have repeatedly shown that people with schizophrenia have large-scale grey matter abnormalities, such as lower grey matter volume. Recent research on improved diffusion MRI (dMRI), genetics, and postmortem evidence, however, indicates that the grey matter of people with schizophrenia may also have microstructural changes. By detecting the diffusion of water molecules in brain tissue, DTI and other diffusion MRI techniques offer indirect evidence of microstructural features. Although these techniques don't evaluate microstructure directly, they can suggest possible changes in the structure of brain tissue [108]. In a study by Park et al., the link between schizophrenia symptoms and microstructural changes in the prefrontal and temporal cortices were examined using DTI [109]. The study found that schizophrenia patients had significantly higher mean diffusivity in the left prefrontal cortex compared to healthy controls, indicating microstructural abnormalities. The study also found that higher positive symptoms observed in schizophrenia patients were correlated with increased mean diffusivity in the left prefrontal and temporal cortices [109]. Microstructural abnormalities in grey matter appear to exist from the onset of the disease and could be connected to the cognitive deficits observed in schizophrenia [110].

Additionally, the relationship between grey matter volume and neurodevelopment may be influenced by gene expression. Ji et al. discovered 98 genes, including DPYD, TRANK1, CTD-SPL2, GATAD2A, and ELAVL2, that control synapse function, neuronal migration and /differentiation, and neurodevelopment

and are substantially linked to changes in grey matter volume in schizophrenia. The expression of these genes was enhanced in schizophrenia brain tissues, supporting their involvement in neurodevelopmental processes. The results reveal neurodevelopmental genes that may contribute to grey matter anomalies in schizophrenia. Although research on the precise timing and course of these microstructural alterations is still ongoing, it is clear how difficult it is to comprehend the neurodevelopmental trajectory of schizophrenia [111].

Choroid Plexus

The blood-cerebrospinal fluid barrier, which separates blood from CSF, is a crucial brain structure that is formed by the choroid plexus (CP), which also produces CSF. It is also essential for immune monitoring and immune responses in the CNS. To regulate brain homeostasis, the CP detects peripheral inflammatory signals and responds by generating cytokines, attracting immune cells, and upregulating immune genes [14]. Neurotrophic factors necessary for brain development, neurogenesis, and neuronal survival are secreted by the choroid plexus [112]. The significance of the CP in neuropsychiatric illnesses, especially schizophrenia, has been the subject of recent research due to increasing evidence of abnormalities in both its structure and function.

Recent studies have emphasized the role and function of the CP in schizophrenia. According to Zeng et al, first-episode antipsychotic-naive schizophrenia patients had a considerably larger CP volume than healthy controls. This study raises the possibility that CP expansion is relevant to schizophrenia onset [113]. The CP regulates CSF secretion and production, which is essential for glymphatic system waste solute drainage and affects CSF flow. The CP is essential for CSF homeostasis and clearing pathways, which is often dysregulated in neurological disorders [114].

Neurotransmitter and chemical imbalances

Neurotransmitter abnormalities, especially in the dopamine and serotonin pathways, have a significant role in schizophrenia [10]. Changes in the serotonergic, dopaminergic, and glutamatergic systems highlight how intricately neurotransmitters are involved in schizophrenia [115]. (Figure 3)

According to the dopamine theory of schizophrenia, psychotic symptoms associated with the disorder are partly caused by dysregulation of dopaminergic neurotransmission, specifically an excess of dopamine D2 receptor signaling [116]. The mesolimbic dopamine pathway, which extends from the nucleus accumbens to the ventral tegmental area, is known to be involved in the positive symptoms of schizophrenia, such as delusions and hallucinations [117]. Elevated activity in the dopaminergic circuit has been suggested to result in skewed perceptions and symptoms of psychosis in schizophrenia patients. Recent neuroimaging data has shifted our understanding of dopamine dysregulation in schizophrenia, highlighting the significant role of the nigrostriatal pathway projecting to the dorsal associative striatum, in addition to the previously emphasized mesolimbic system, though ongoing research continues to refine our understanding of the relative contributions of different dopaminergic pathways in schizophrenia [118]. Cortical areas involved in cognitive processes including attention and significance processing, such as the anterior cingulate cortex and dorsolateral prefrontal cortex, provide inputs to the dorsal striatum [117]. Dysfunction of the dorsal striatum and dopaminergic pathway dysfunction in the nigrostriatal routes are possible factors leading to the pathophysiology of schizophrenia. Evidence supports the dopamine theory in schizophrenia, with antipsychotic medications blocking D2 dopamine receptors, causing a decrease in dopamine levels. Neuroimaging shows altered dopaminergic activity in schizophrenia patients, with amphetamines causing exacerbated symptoms [119]. However, dopamine dysregulation is not the only factor in schizophrenia's complex etiology.

Antipsychotic drugs, which are essential for the treatment of schizophrenia, work by blocking dopamine receptors to lessen the symptoms of the illness. Antipsychotics can also have complex, differential effects on different dopaminergic pathways and do not always lower total dopamine levels, which could result in different therapeutic outcomes and adverse effects in different patients [120]. In addition, the blockage of dopamine D2 receptors in the nigrostriatal dopamine pathways by antipsychotics can cause extrapyramidal symptoms (EPS), which encompasses disorders like tardive dyskinesia, parkinsonism, akathisia, and dystonia [121,122]. PET studies have shown a direct association between the intensity of EPS and D2 receptor occupancy in the substantia nigra, indicating a correlation between the therapeutic and side effects of antipsychotics. A greater antipsychotic effect, indicated by high D2 receptor occupancy, can also lead to greater side effects, including motor dysfunction [123].

Serotonin is another neurotransmitter involved in reward processing that is highly implicated in schizophrenia pathology. Schizophrenia has been linked to serotonin malfunction, specifically involving serotonin 6 and 7 receptors. It has been suggested that serotonin 6 and 7 receptors influence brain plasticity and neurotransmitter systems including glutamate and dopamine, which may contribute to schizophrenia. The role of serotonin 6 and 7 receptors in regulating glutamate and dopamine signalling indicates that these receptors could serve as a target for the treatment of schizophrenia, with the potential to treat both the disorder's positive symptoms, such as hallucinations, and negative symptoms like lack of emotional expression [8,124]. Serotonin's role in schizophrenia has been further clarified by studies on serotonin 2A receptors. The majority of antipsychotic drugs work by antagonistically binding to the serotonin 2A (5-HT2A) receptor, which is central to the pathophysiology

of schizophrenia. Abnormalities in 5-HT2A's expression and activity contribute to psychotic symptoms [125,126]. Serotonin's early involvement in schizophrenia is shown by decreased densities of 5-HT2A receptors in the frontal lobe of patients relative to healthy subjects [127]. Abnormal serotonergic activity is not limited to the early phases or high-risk people, but rather occurs over the whole spectrum of schizophrenia [128].

Glutamate, the main excitatory neurotransmitter, is crucial to the pathophysiology of schizophrenia and is involved in negative symptoms and cognitive deficits. N-methyl-d-aspartate (NMDA), a type of glutamate receptor, can aggravate negative and positive symptoms in people who already have schizophrenia and induce symptoms like those of schizophrenia in healthy subjects [129]. As a result, glutamatergic neurotransmission disruption has been identified as a possible target for medication development [130]. The glutamatergic and NMDA receptor dysfunction theories of schizophrenia have been extensively studied using pharmacological models, which involve the injection of psychotomimetic drugs such as phencyclidine (PCP) and ketamine [131]. Abnormal dendrites and decreased levels of the axon marker synaptophysin were observed in glutamatergic neurons of post-mortem cerebral cortical tissue from individuals with schizophrenia, signifying significant axonal damage in glutamatergic pathways [132].

A protein complex called the cystine/glutamate antiporter Xc^- exchanges intracellular glutamate for cystine, preserving antioxidant defences and affecting excitatory neurotransmission [133]. In schizophrenia patients, downregulation of the Xc^- subunits SLC7A11 and SLC3A2 has been observed, suggesting a possible connection to the pathophysiology of schizophrenia [133]. Assessing the expression levels of Xc^- subunits in peripheral blood cells may be a new way to identify schizophrenia biomarkers, as it reflects dysregulated glutamate and antioxidant systems. Blocking Xc^- could decrease excessive glutamate release and excitotoxicity as well as improve glutathione synthesis and counteract oxidative stress [134,135]. To confirm Xc^- as a trustworthy biomarker and assess Xc^- modulators as a possible schizophrenia therapy, further research on the relationship between Xc^- and schizophrenia is required [133].

Discussion

Current pharmacological therapies frequently struggle to achieve a balance between side effects and efficacy, which makes long-term care and medication compliance difficult. Treatment for schizophrenia appears to have a bright future with an emphasis on creating individualized plans and focused therapies.

Leading biopharmaceutical startup Karuna Therapeutics is creating innovative therapies for schizophrenia and other mental illnesses. Their primary medication, KarXT, targets the cholinergic system, which has been connected to schizophrenia's cognitive and psychotic symptoms [136]. Positive findings from phase 2 clinical trials highlight the significance of concentrating on distinct neurotransmitter systems to create novel neurological drugs. Promising outcomes for treating schizophrenia are revealed by a critical study of the pre-clinical and early clinical data of KarXT. Weiden et al. found that KarXT exhibited considerably greater response rates when compared to placebo. Notably, reductions in schizophrenia symptoms were observed across all categories as early as two weeks into the treatment. This implies that KarXT may be effective for treating a wide range of schizophrenia symptoms and may also have a quick start of action [137]. Although the KarXT research, a novel treatment for schizophrenia, has produced encouraging results, its ambiguous long-term effects pose difficulties. Concerns of negative consequences are raised by the study's early stage of clinical testing. Prospects for the future appear cautiously positive, since individuals who are resistant to dopaminergic therapy may benefit from a novel therapeutic avenue because to KarXT's distinct mode of action. To fully evaluate KarXT's efficacy and safety profile, however, as well as to assess if incorporating it into the current schizophrenia treatment modalities is possible, larger-scale phase 3 clinical trials are necessary. Preclinical studies, such as those using animal and cognitive models, have improved our knowledge of the pathophysiology and potential therapeutic targets of schizophrenia. However, accurate translation of preclinical research findings into clinical practice requires more robust prediction models and genetic variation.

The incorporation of genetic research, specifically focusing on CNVs, has the potential to yield more customized therapeutic approaches and improved treatment responses. The possible involvement of immune dysfunction and structural alterations in the brain in the pathophysiology of schizophrenia has also led to the investigation of immune-modulating pharmaceuticals in addressing neuroinflammation and immune system abnormalities observed in schizophrenia pathology. Moreover, structural and functional alterations in areas of the brain, including the thalamus, basal ganglia, and prefrontal cortex, have been identified by brain imaging studies as contributing to the disorder's behavioural and cognitive symptoms. Comprehending these intricate connections between genetics, immunology, and brain architecture could open up novel opportunities for therapeutic targets and interventions that could greatly enhance the quality of life for those who suffer from schizophrenia.

Conclusion

The diverse aspects of schizophrenia have been examined in this paper, which has integrated knowledge from studies on genetics, immunology, neuroanatomy, and treatments. The intricate interactions among copy number variations, immune dysfunction, aberrant synaptic pruning, and neurotransmitter imbalances highlight the diversity in the etiology and pathogenesis of schizophrenia. Considerable progress in comprehending

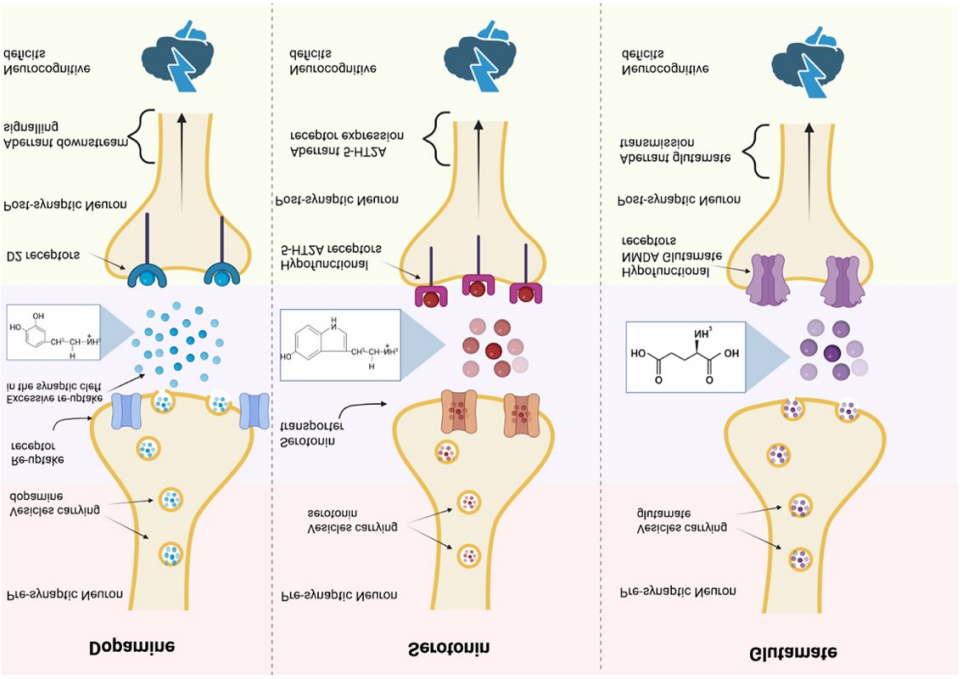

Fig. 3 Dopamine, Serotonin and Glutamate abnormalities in Schizophrenia — Positive symptoms of schizophrenia, such cleft. Increased sensory sensitivity, paranoid thinking, and trouble telling the difference between truth and fantasy are possible symptoms for patients [116,119]. Changes in mood, perception, and cognition may result from the dysfunction of serotonin 5-HT2A receptors. Negative symptoms of schizophrenia include emotional homogeneity, social disengagement, and motivation deficits. Additionally, cognitive deficiencies, such as issues with executive functioning, memory, and attention, can be attributed to malfunctioning 5-HT2A receptors [125,126]. In schizophrenia, hypofunctional NMDA receptors can cause a variety of cognitive and perceptual abnormalities. Individuals may struggle with social cognition, memory development, and learning. In addition to causing emotional symptoms and cognitive deficiencies, this disturbance of glutamate signalling may also result in issues with attention, working memory, and executive function [129].

the function of genes like C4A and CNVs like the deletion of 22q11.2 has opened up novel insights on the neurological basis of the illness.

Novel antipsychotic formulations and delivery strategies are among the recent pharmacological advancements that provide hope for increased treatment efficacy and adherence. However, obstacles persist, specifically with the management of treatment-resistant schizophrenia and the adverse and cognitive manifestations of the illness. The rise of personalized medicine approaches based on genetic and neurobiological markers has the potential to lead to more targeted and effective interventions.

Future studies should focus on better understanding the intricate connections between genetic predisposition, environmental circumstances, and neurobiological mechanisms in schizophrenia. Furthermore, turning these findings into clinically relevant diagnostic tools and therapeutic procedures remains a vital objective. As our understanding of schizophrenia grows, interdisciplinary collaboration will be critical in creating comprehensive ways to diagnose, treat, and potentially prevent schizophrenia.

Methods

A thorough evaluation of the literature on schizophrenia, emphasizing the roles of neurological, immune, therapeutic, and genetic aspects was performed. The inclusion of reliable, peer-reviewed papers with a focus on primary research published in the field by using PubMed as the main literature database was ensured. The following individual keywords were used in a series of systematic searches: ”Copy Number Variants,” ”Schizophrenia Neuroimaging Studies,” ”Immune Dysfunction,” ”Schizophrenia Pathology,” ”Synaptic pruning,” and ”Genetics, with no Boolean operators.

Limitations on English-language papers and an emphasis on publications over the last 20 years were two other evaluation criteria. To mitigate potential limitations, such as inherent differences in schizophrenia research and the potential for publication bias, the investigator investigated several study designs and scrutinized inconclusive findings in the literature. By integrating information from neurological, immune, genetic, and therapeutic studies, hoping to provide a detailed and systematic summary of the current understanding of schizophrenia pathogenesis. This

comprehensive review relied only on keyword-based searches to compile pertinent material to condense discoveries in the field and advance knowledge of the intricate nature of schizophrenia.

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