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Stem Cells in Schizophrenia: A Game-Changer or Science Beyond Reach

Swarup K. Chakrabarti[1]* and Dhrubajyoti Chattopadhyay[1,2]

[1]*H. P. Ghosh Research Center, New Town, Kolkata, West Bengal 700161, India.*

[2]*Sister Nivedita University, New Town, West Bengal 700156, India.*

**Corresponding author: Swarup K. Chakrabarti.*

Abstract

Schizophrenia (SCZ) is a severe mental disorder that greatly impacts society. This article looks at the neurobiological mechanisms of SCZ, including abnormal NMDA receptor function, changes in glutamate levels, and genetic influences like DTNBP1 and NRG1, which lead to cognitive impairments and episodes of psychosis. Stem cell therapies show promise in addressing neurodevelopmental and neurochemical issues in SCZ, aiming to promote neurogenesis, improve myelin formation, and enhance synaptic functions. Gene editing techniques, such as CRISPR, could tailor treatments by correcting genetic mutations. However, challenges such as cell integration issues, immune responses, and regulatory hurdles remain, underscoring the need for further research to improve and implement these therapies for more effective and personalized care.

Keywords: schizophrenia; stem cell therapies; neural connection; neurogenesis; behavioral disorders

Introduction

Schizophrenia (SCZ) is a serious psychiatric disorder that affects about 1% of the worldwide population [1]. Though its occurrence is relatively rare, it has a significant impact on both individuals and society due to its debilitating characteristics. The condition is marked by various symptoms, including hallucinations, delusions, disorganized speech, chaotic behavior, cognitive deficits, and negative symptoms like diminished emotional expression, a flat affect, and reduced motivation. These obstacles often lead to challenges in sustaining relationships, holding jobs, and living independently, which can result in social isolation, impaired functioning, and a heightened risk of early death [2-4]. The effects of SCZ also affect caregivers, who frequently endure considerable financial pressure due to healthcare costs and repeated hospital stays. The requirements of caregiving can restrict job prospects, leading to a decrease in household earnings, while the emotional stress, characterized by anxiety and burnout, adds to their difficulties. Stigma additionally marginalizes caregivers, resulting in a lack of support, which creates a dual challenge of financial and social difficulties that underscores the wider societal consequences of the disorder [5-7]. From a broader perspective, SCZ significantly contributes to the global disease burden, resulting in healthcare costs and decreased productivity that strain economic systems [8, 9]. The disorder typically presents itself during late adolescence or early adulthood, with genetic predispositions and environmental factors like prenatal stress, childhood trauma, and cannabis use playing key roles in its development [2-4, 10, 11].

In individuals with SCZ, a prodromal phase is present in 80-90% of cases, characterized by a gradual emergence of less severe or sub-threshold symptoms [10-13]. These initial symptoms are thought to fall along a spectrum that leads to the full development of delusions and hallucinations commonly associated with the condition. The differentiation between the prodromal phase and psychotic episodes occurs when these symptoms become more frequent, widespread, and debilitating, causing the person to lose awareness of the false nature of their beliefs and experiences [2-4, 10-13]. While the length of this phase can differ, it usually lasts around a year. More than half of those diagnosed with SCZ suffer from several comorbid mental and physical conditions, making the treatment and care processes more complex [14, 15]. The roughly 60% concordance rate for SCZ among monozygotic twins underscores the significant impact of environmental factors in determining how genetic vulnerability manifests in this disorder [16, 17]. Various environmental influences, including childbirth complications, early-life challenges, urban upbringing, and migrant background, are believed to

interact with genetic tendencies to heighten the risk of developing SCZ [18]. The neurodevelopmental hypothesis of SCZ suggests that an interplay of genetic risks and environmental factors during the early stages of brain development sets the groundwork for the emergence of symptoms in early adulthood. These factors, especially prominent during the prenatal and early years, emphasize the vital need for early interventions and comprehensive approaches to alleviate the effects of SCZ on individuals, families, and society [19, 20].

The clinical symptoms associated with SCZ are generally divided into three categories: positive symptoms (such as hallucinations, delusions, and disorganized thoughts), negative symptoms (including lack of motivation, flat affect, and social withdrawal), and cognitive symptoms (like memory deficits and challenges with attention and executive function) [2-4, 10-13]. These symptoms are believed to result from changes in brain chemistry, primarily affecting dopamine and glutamate neurotransmission. The dopaminergic hypothesis posits that heightened dopamine activity in the mesolimbic system contributes to positive symptoms, while diminished dopamine activity in the mesocortical pathway is associated with negative symptoms [21, 22]. Additionally, the glutamatergic hypothesis highlights the dysfunction of glutamate signaling, particularly through NMDA (N-methyl-D-aspartate) receptors, which leads to compromised neural connectivity, notably in the prefrontal cortex. This dysfunction is thought to contribute to cognitive impairments. Together, these theories offer a framework for comprehending the intricate neurobiological foundations of SCZ, involving both disrupted dopamine and glutamate systems that affect various brain regions and their functions [23, 24]. SCZ is a chronic illness that necessitates continuous care, even when symptoms show improvement. Although there is no definitive cure at this time, a combination of medication and therapy is crucial for managing symptoms [25, 26]. Antipsychotic medications, which play a vital role in treatment, mainly affect neurotransmitter functions in the brain, with a particular emphasis on dopamine and serotonin receptors. These drugs are thought to ease symptoms by normalizing the activity of these key neurotransmitters, which have an impact on mood, cognition, and perception [27, 28].

In some instances, particularly if symptoms escalate or during a crisis, hospitalization may be required for stabilization and close monitoring. It is crucial to highlight the importance of adhering to medication, as stopping treatment can result in a relapse, even if symptoms seem to have temporarily improved. Moreover, psychosocial therapy can assist in long-term recovery by supporting individuals in coping with their condition and enhancing their overall quality of life [29, 30]. While existing treatments for SCZ mainly aim to reduce symptoms without offering a cure, emerging research is beginning to investigate potential breakthroughs that could transform both neuroscience and psychiatry. One of the most promising directions is stem cell therapy, which may provide a curative option rather than remaining purely theoretical. Given their capability to differentiate into diverse cell types, stem cells might contribute to the repair or replacement of damaged neural circuits associated with the disorder. This strategy could tackle the fundamental biological issues related to SCZ, leading to more effective and enduring treatments that prioritize recovery over mere symptom management. As progress in this field continues, stem cell-based therapies might ultimately deliver true hope for a real cure, significantly changing how SCZ and other neuropsychiatric conditions are addressed [31-33]. Against this backdrop, this article aims to provide an in-depth analysis of the mechanistic insights and innovative developments that highlight the potential of stem cell therapies as a revolutionary approach to treating SCZ. It underscores the promise of early intervention strategies, utilizing stem cell-based methods to address the condition in its initial stages, guided by new understanding of the disease's early signs and fundamental biology.

Schizophrenia: Pathophysiology and Underlying Mechanisms

SCZ is a multifaceted disorder with a complex pathophysiology that continues to challenge researchers [1-4]. Decades of investigation have revealed that its origins involve numerous genetic and neurobiological factors, many of which remain to be fully elucidated. Genetic studies have highlighted the highly polygenic nature of SCZ, implicating hundreds to thousands of distinct genetic loci [34-36]. Genome-wide association studies (GWAS) have uncovered over 100 specific loci, each with varying effects, underscoring the disorder's genetic complexity [37, 38]. Interestingly, these genetic risks demonstrate significant pleiotropy, meaning that certain genetic variants are shared across other neuropsychiatric

conditions, including bipolar disorder, major depressive disorder, and autism spectrum disorder (ASD) [39, 40]. Among the key neurotransmitter systems implicated in SCZ, dopamine has long been recognized as central to the manifestation of psychotic symptoms. The dysregulation of dopaminergic signaling, influenced by genetic predispositions, plays a pivotal role in shaping the disease's clinical presentation [21-23]. Prominent candidate genes linked to SCZ include *COMT* (catechol-O-methyltransferase), *DISC (Disrupted-in-Schizophrenia)*, *RGS4* (Regulator of G-protein signaling 4), *PPP3CC* (Protein Phosphatase 3 Catalytic Subunit Gamma), ZDHHC8 (Zinc Finger DHHC-type palmitoyltransferase 8), *AKT1* (AKT Serine/Threonine Kinase 1), and α7nAChR (Alpha-7 Nicotinic Receptor Genes), among others [41-43]. These genes are associated with various regulatory mechanisms, such as synaptic plasticity, intracellular signaling pathways, and neurotransmitter metabolism, particularly involving dopamine [44, 45]. Notably, the Dystrobrevin Binding Protein 1 (DTNBP1) and Neuregulin 1 (NRG1) genes have emerged as especially compelling candidates due to their robust associations with SCZ in multiple studies [46-48]. Both genes are integral to synaptic function within the central nervous system (CNS), with particular importance in modulating glutamatergic neurotransmission. Glutamate, alongside dopamine, is increasingly recognized for its role in the pathophysiology of SCZ, contributing to cognitive and perceptual disturbances [49, 50]. Research into the functions of DTNBP1 and NRG1 has revealed their influence on neural circuit development and synaptic maintenance. For instance, DTNBP1 is involved in synaptic vesicle trafficking and may indirectly regulate dopamine release, while NRG1 plays a critical role in neurodevelopmental processes, such as neuronal migration and myelination. Dysfunction in these pathways can lead to abnormalities in neural connectivity and neurotransmitter balance, hallmarks of SCZ [51-53]. While the precise mechanisms underlying these genetic associations remain a topic of ongoing study, advancements in genomic technologies and neurobiological research continue to provide insights into how these genes interact with environmental factors. Understanding the interplay of these elements may pave the way for novel therapeutic interventions targeting the underlying molecular drivers of SCZ.

Glutamate, as the primary excitatory neurotransmitter in the CNS, plays an essential role in normal brain function, particularly in synaptic transmission, learning, memory, and neuroplasticity. It is the amino acid with the highest concentration in the brain, with levels ranging between 5-15 mmol/kg of brain tissue, highlighting its prevalence and importance [54, 55]. Most synapses use glutamate to propagate excitatory signals across neural circuits. However, its physiological concentration must be finely tuned. Both low and high levels of glutamate can have detrimental effects. Excessive glutamate, if not carefully regulated, can lead to excitotoxicity—a process where overstimulation of neurons causes cell damage or death. This mechanism is implicated in various neurodegenerative conditions, including SCZ [56-60]. In the study of SCZ, disturbances in glutamate signaling—particularly involving NMDA receptors—have become a crucial focus for research. The NMDA receptor, a form of glutamate receptor, plays an essential role in enabling synaptic plasticity, neuronal communication, and higher cognitive functions like learning and memory [61-63]. It operates by allowing calcium, sodium, and potassium ions to enter the postsynaptic cell when glutamate binds, initiating complex intracellular signaling cascades that affect synaptic strength and the connections within neural networks. This receptor is particularly important for regulating long-term potentiation (LTP), which is associated with memory formation and cognitive abilities [64, 65].

The malfunction of NMDA receptors in SCZ disturbs the balance between excitatory and inhibitory neurotransmission, particularly impacting GABA (gamma-aminobutyric acid) ergic interneurons that usually regulate excessive neuronal activity. This disturbance leads to heightened excitability in neural circuits, contributing to the disorganized thought processes, hallucinations, and delusions characteristic of the condition [66-68]. Additionally, reduced function of NMDA receptors can cause elevated glutamate levels, particularly in the prefrontal cortex and hippocampus, which may overactivate non-NMDA receptors, leading to excitotoxicity and exacerbating cognitive dysfunction. The deficits in synaptic plasticity and neuroplasticity associated with NMDA receptor dysfunction are correlated with structural alterations in the brain, such as reduced gray matter volume in critical regions [69, 70]. To sum up, SCZ is influenced by both genetic and neurobiological factors, with dysfunctional NMDA

receptor activity being central to the condition. Disruption of glutamate signaling interferes with the balance between excitatory and inhibitory signals, resulting in symptoms such as hallucinations and cognitive impairment. Increased glutamate levels lead to excitotoxicity, worsening neuronal injury. Genes such as DTNBP1 and NRG1 underscore the significance of synaptic functioning and glutamatergic signaling in the context of SCZ.

Mechanisms of Stem Cell Therapy for Schizophrenia

Stem cell therapies present a promising avenue for addressing the intricate and multifactorial pathophysiology of SCZ. This strategy seeks to confront the fundamental neurodevelopmental and neurochemical deficiencies linked to the disorder by using the regenerative capabilities of stem cells [71-74]. The ways in which stem cells might provide therapeutic benefits for SCZ are diverse and encompass several important processes, such as reinstating neurogenesis, regulating synaptic activity, rectifying immune system imbalances, and facilitating precision medicine approaches [75, 76]. SCZ is often associated with a reduction in neurogenesis, particularly in regions such as the hippocampus and prefrontal cortex, which are crucial for memory, cognition, and emotional regulation [77]. Stem cell-based therapies aim to address these deficits by introducing neural stem cells (NSCs) **or** induced pluripotent stem cells (iPSCs) into affected areas. These stem cells can differentiate into neurons, glial cells, and other brain components, replenishing lost or damaged cells and potentially reversing cognitive and emotional impairments [78-80]. Stem cell therapies have the potential to enhance myelination issues, especially in disorders like SCZ, where disruptions in brain development are associated with myelination impairments [81, 82]. Oligodendrocyte precursor cells (OPCs), which are the main progenitors of oligodendrocytes responsible for the formation of myelin, can be derived from stem cells, including iPSCs and mesenchymal stem cells (MSCs) gathered from human umbilical cord blood (hUC-MSCs) [83-85]. These stem cells might address myelination issues by facilitating the differentiation of OPCs into mature oligodendrocytes that can create functional myelin sheaths around neuronal axons.

In the case of SCZ, stem cell therapies could help restore typical myelination patterns, particularly in areas such as the prefrontal cortex, where myelination occurs later in life and often presents deficits in those with SCZ [86-88]. By promoting the differentiation and maturation of OPCs, these treatments may effectively tackle myelination disruptions that arise during crucial developmental phases like childhood and adolescence. Moreover, stem cell therapies might strengthen the integrity of white matter (WM) pathways, which are crucial for effective neuronal communication [89, 90]. WM, made up of myelinated axons, allows for quick signal transmission between various brain areas. In cases of SCZ, disruptions in white matter integrity can hinder connectivity and lead to cognitive deficits. By enhancing the health of WM pathways, stem cell treatments could foster improved neuronal communication, resulting in advancements in cognitive functions and overall brain performance [91-93]. One of the main therapeutic goals of stem cell-based approaches is to restore synaptic function, which is often disrupted in SCZ [94, 95]. Synaptic plasticity—the brain's ability to strengthen or weaken synaptic connections over time—plays a central role in cognitive processes, and its dysfunction is a hallmark of the disorder. Stem cell-derived neurons have the potential to integrate into existing neural circuits and form new, functional synapses, thereby improving communication between neurons. This could repair deficits in synaptic plasticity, particularly in brain regions such as the prefrontal cortex, which are involved in higher cognitive functions like working memory, decision-making, and emotional regulation [96, 97].

For instance, a research study conducted by Brennand and colleagues employed iPSCs obtained from individuals with SCZ to produce neurons *in vitro* [98]. These derived neurons demonstrated deficits in synaptic plasticity when compared to neurons from control subjects. However, following the transplantation of these iPSC-derived neurons into the brains of rodents, they successfully assimilated into existing neural circuits, established functional synapses, and revitalized synaptic activity. This integration enhanced communication between neurons, indicating a possible mechanism for restoring impaired synaptic function in SCZ. Scientists also examined the impact of introducing neurons derived from NSCs into the prefrontal cortex of mice exhibiting symptoms similar to SCZ. The findings revealed that the transplanted neurons established functional synaptic connections and LTP. This recovery of LTP correlated with enhancements in working memory and decision-making—cognitive abilities that are usually compromised in individuals

with SCZ [99, 100]. SCZ is also linked to neuroinflammation, characterized by the abnormal activation of microglia and elevated levels of pro-inflammatory cytokines [101, 102]. These factors contribute to neuronal dysfunction and cognitive deficits. Stem cells, MSCs, and iPSCs have shown promise in modulating the immune response [103-105]. They secrete cytokines and other molecules that reduce microglial activation, potentially alleviating the neuroinflammation associated with the disorder. This immune-modulating effect could help restore a more balanced brain environment, promoting neuronal survival and function.

For instance, in a rodent model of SCZ involving maternal immune activation (MIA), the offspring displayed behaviors indicative of anxiety and signs of neuroinflammation, characterized by the activation of microglia and changes in synaptic protein levels [106, 107]. Treatment with human hUC-MSCs significantly reduced these symptoms. hUC-MSCs influenced microglial function and regulated various molecules such as IBA1 (Ionized Calcium Binding Adaptor Molecule), HMGB1 (High Mobility Group Box 1), and PSD95 (Postsynaptic Density Protein 95), facilitating synaptic repair and decreasing inflammation [108-110]. These results imply that hUC-MSCs could provide a promising therapeutic strategy for SCZ by addressing behavioral and neuroinflammatory issues. Moreover, stem cell therapies may aid in restoring the blood-brain barrier (BBB), which is often compromised in SCZ, thereby reducing the infiltration of harmful inflammatory mediators into the brain [111-113]. Recent studies indicate that methods utilizing stem cells, such as the transplantation of neural progenitor cells (NPCs), may help in restoring the integrity of the BBB by enhancing the production of tight junction proteins, which are crucial for sustaining the barrier's selective permeability [114-116]. For example, research conducted on animal models has shown that endothelial cells derived from stem cells can enhance BBB function and decrease neuroinflammation, consequently alleviating the neurovascular disruptions linked to SCZ [117-119]. Stem cell-based therapies also hold promise for personalized treatment through the integration of gene editing techniques, such as CRISPR (clustered regularly interspaced short palindromic repeats)-Cas9 (CRISPR-associated protein 9) [120, 121]. SCZ has a complex genetic foundation, with several susceptibility genes implicated in its onset, including DISC1, NRG1, and COMT. Gene editing allows for the correction of mutations in iPSCs derived from a patient's own cells, ensuring that the stem cells generated are genetically tailored to the individual [122-124]. This precision medicine approach not only targets the genetic causes of SCZ but also minimizes the risk of immune rejection and improves treatment efficacy.

For stem cell therapy to be effective, the transplanted cells must integrate functionally into existing neural circuits [125, 126]. This requires stem cells to differentiate into appropriate cell types and establish meaningful synaptic connections with surrounding neurons. The long-term survival and proper integration of these cells are critical for achieving sustained therapeutic effects. Over time, functional integration of stem cells into the brain's networks could help restore normal cognitive function and alleviate SCZ symptoms, improving both memory and emotional regulation. Additionally, stem cells may contribute to the rejuvenation of aging or degenerated brain regions, enhancing not just cognitive function but also emotional and social behaviors. This comprehensive approach offers the potential for long-lasting benefits, promoting the restoration of neural circuits and improving the overall architecture of the brain, which is foundational for mental health and cognition [127, 128]. By combining gene editing with stem cell therapy, the root genetic causes of SCZ can be addressed in a personalized manner. This approach enables the correction of individual genetic mutations, enhancing the efficacy of treatments while reducing potential side effects. Ultimately, the use of gene editing and stem cells may shift the treatment paradigm of SCZ from symptom management to a curative, individualized approach, offering hope for more effective and lasting therapies.

Stem Cell-based Approaches in SCZ Treatment: Challenges and Limitations

One of the prominent approaches in cell therapy for treating SCZ is the implantation of interneurons, which has sparked considerable interest as a potential treatment method [129, 130]. This process involves introducing inhibitory neurons into the brain to help restore equilibrium in neural circuits that may be disrupted in conditions like SCZ. Interneurons are essential for maintaining the brain's excitatory-inhibitory balance, and their successful integration could potentially reduce some of the cognitive and behavioral challenges linked to the disorder [131, 132]. Nevertheless, several obstacles and limitations

temper the excitement surrounding these encouraging findings.

One significant challenge is the lack of a clear biomarker to assess an individual's likelihood of developing SCZ. In the absence of these biomarkers, preventive measures like cell transplants encounter considerable obstacles to their clinical implementation. Furthermore, the effectiveness of interneuron transplants relies on a comprehensive understanding of how these transplanted cells merge with existing neural networks and bring about therapeutic benefits. This requires tackling essential questions regarding the functional connectivity of transplanted interneurons and their capacity to properly modulate neuronal activity. Additionally, there are considerable scientific obstacles that need to be addressed. A primary concern is the potential for tumor formation, as transplanted cells might result in undesirable growths or cancers, especially when the cells are obtained from pluripotent origins [133]. Furthermore, regulatory challenges represent another significant issue. The lengthy duration required for clinical trials, along with the intricate nature of the procedures and the necessity for thorough safety evaluations, may hinder the application of these therapies in clinical settings [134]. Moreover, the substantial costs linked to these advanced treatments, as well as difficulties in sourcing and maintaining adequate quantities of cells for extensive clinical use, pose considerable challenges to their widespread implementation. Although these obstacles exist, the preclinical findings are still quite persuasive. Nevertheless, in order to move from experimental models to effective therapies for patients, it will be crucial to address these scientific, regulatory, and logistical challenges. Only after doing so can stem cell-derived neural transplants be regarded as a practical and enduring solution for treating SCZ.

Future directions

Combining stem cell therapies with innovative gene editing technologies has great potential to improve SCZ treatment. Future studies should aim to employ CRISPR/Cas9 and other gene-editing methods to rectify genetic alterations linked to SCZ in stem cells derived from patients, offering a possible approach to create healthy neural cells and reestablish disrupted neural circuits. Precision gene editing could also be utilized to fine-tune stem cell differentiation, improving the development of specific types of neurons or glial cells that are functionally impaired in individuals with SCZ. Integrating pharmacological approaches with stem cell therapy presents an intriguing opportunity for future research. GLP-1 (Glucagon-Like Peptide-1) receptor agonists (GLP-1RAs), recognized for their protective effects on nerve cells, have demonstrated promise in alleviating neuropsychiatric symptoms linked to SCZ [135, 136]. Future studies should examine the combined impact of activating GLP-1R alongside stem cell therapies to enhance both symptom alleviation and neuronal restoration [137, 138]. These multifaceted strategies may address both the fundamental cellular impairments and provide relief from cognitive and emotional challenges. Additionally, the progress in brain simulation technologies, such as non-invasive brain stimulation and cutting-edge neuroimaging methods, may aid in customizing stem cell-based interventions [139, 140]. By outlining the individual patient's distinct neural networks, personalized therapeutic strategies can be crafted to enhance the effectiveness of stem cell therapies. This patient-centered strategy, along with new biomarkers and neural data, would enable the development of more accurate, tailored treatments that improve treatment results. In summary, the integration of gene editing, stem cell treatments, pharmacological therapies, and cutting-edge neurotechnology has the potential to significantly change the landscape of SCZ treatment. It is crucial to conduct collaborative, multidisciplinary research to explore these promising pathways and translate them into clinical practice for enhanced patient care.

Conclusion

Stem cell-based therapies for SCZ represent a promising frontier in treatment, potentially addressing core neurodevelopmental and neurochemical deficits associated with the disorder. These therapies hold the potential to restore neurogenesis, rectify myelination issues, and improve synaptic function, offering the possibility of improving cognition, memory, and emotional regulation in SCZ patients. However, significant challenges remain, including the need for better understanding of cell integration, immune responses, and the precise mechanisms of action. Additionally, ethical, safety, regulatory, and cost-related issues must be carefully addressed to make these therapies viable in clinical practice. With continued research and technological advances, stem cell-based treatments

could ultimately provide a more effective and personalized approach to managing SCZ, but more work is needed before they can be widely implemented.

Declarations

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Conflict of Interest

The authors declare no conflict of interest.

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