Journal of Medical and Health Studies
ISSN: 2710-1452
DOI: 10.32996/jmhs
Journal Homepage: www.al-kindipublisher.com/index.php/jmhs

JMHS
AL-KINDI CENTER FOR RESEARCH AND DEVELOPMENT

| RESEARCH ARTICLE

Applications of single-cell sequencing in schizophrenia research

Yuxin Huang
College of Life Sciences, Northeast Agricultural University, Harbin City, Heilongjiang Province, China
Corresponding Author: Yuxin Huang, **Email:** 961549383@qq.com

| ABSTRACT
Schizophrenia (SCZ) is a highly heritable, severe neuropsychiatric disorder characterized by complex genetic architecture and heterogeneous clinical manifestations. Despite decades of research, the precise molecular and cellular mechanisms underlying its pathogenesis remain incompletely elucidated, which significantly hinders the development of effective preventive strategies and complicates treatment approaches. This comprehensive review systematically examines the emerging application of cutting-edge single-cell sequencing technologies in SCZ research. Single-cell sequencing serves as an unprecedented high-resolution molecular microscope, providing researchers with the remarkable ability to distinguish and characterize the minute individual cellular and molecular components that constitute the extraordinarily complex SCZ "puzzle". The systematic integration of these diverse molecular fragments into a unified, coherent pathophysiological framework holds tremendous promise for yielding transformative research advancements that could fundamentally alter our approach to SCZ diagnosis, treatment, and prevention.

| KEYWORDS

Single-cell sequencing; Schizophrenia (SCZ)

| ARTICLE INFORMATION

ACCEPTED: 01 November 2025 **PUBLISHED:** 07 November 2025 **DOI:** 10.32996/jmhs.2025.6.6.6

Introduction

Schizophrenia (SCZ) is a debilitating and complex psychiatric condition that presents with a constellation of positive and negative symptoms. The positive symptoms, which are more overt and readily recognizable, include perceptual disturbances such as auditory or visual hallucinations, fixed false beliefs (delusions), and markedly disorganized speech and behavior. In contrast, negative symptoms represent subtle yet profound deficits in normal mental functioning, encompassing diminished emotional expression (affective flattening), poverty of speech and thought (alogia), reduced motivation (avolition), and impaired ability to experience pleasure (anhedonia).

Clinical observations indicate that while positive symptoms may be more prominent in the early stages of illness, negative symptoms tend to become increasingly predominant as the disorder progresses. Notably, a subset of patients may initially present with exclusively negative symptoms, which poses significant diagnostic challenges. These negative symptoms are frequently overlooked or misattributed to other causes by both patients and clinicians alike, resulting in substantial delays in accurate diagnosis and initiation of appropriate therapeutic interventions for individuals with SCZ.

Compounding these clinical difficulties is the widespread public misunderstanding that erroneously equates "schizophrenia" with "split personality" disorder. This persistent misconception fosters social stigma and discrimination against affected individuals, creating substantial barriers to treatment. Many patients consequently experience profound reluctance to acknowledge their symptoms or pursue psychiatric care, further exacerbating the personal and societal burden of this severe mental illness. The combination of diagnostic challenges and societal stigma underscores the critical need for enhanced public education and improved clinical recognition of schizophrenia's diverse symptomatology.

Schizophrenia (SCZ) patients demonstrate profound and multifaceted psychological disturbances, prominently featuring emotional instability characterized by rapid mood swings, pronounced social withdrawal leading to isolation, pervasive suspiciousness that may border paranoia, and a marked reduction in volitional capacity affecting motivation and goal-directed behavior. These psychological manifestations are accompanied by substantial neuroanatomical abnormalities, including a notable decrease in total brain parenchymal volume, significant enlargement of the lateral ventricular spaces, and widespread disruptions in the functional connectivity of critical neural circuits[1]. Despite extensive research efforts, the precise genetic architecture that gives rise to this complex constellation of symptoms continues to evade definitive identification. The progressive refinement of SCZ investigation methodologies, transitioning from macroscopic tissue analyses to sophisticated cellular-level examinations, has revealed the intricate cellular pathology underlying this disorder, thereby establishing a crucial foundation for more targeted genetic and molecular exploration [1]in subsequent research phases. While high-caliber studies that establish direct causal relationships between single-cell sequencing findings and SCZ pathogenesis are still in their developmental stages, this cutting-edge technological approach has already revolutionized our comprehension of disease-specific cellular populations and their pathological secretory dysfunctions in SCZ, including but not limited to significant imbalances in neurotransmitter systems and dysregulated immune–inflammatory mediator release[2]. Although absolute prevention of SCZ onset remains beyond current medical capabilities, evidence-based preventive strategies and early interventions can dramatically diminish the likelihood of disease manifestation, postpone its initial appearance, or substantially ameliorate the intensity of symptomatic expression when the disorder emerges.

2. Applications of single-cell sequencing in schizophrenia research

2.1 Research findings

A groundbreaking study conducted by a collaborative research team from prestigious institutions such as Harvard University and the Massachusetts Institute of Technology (MIT) employed advanced single-nucleus RNA sequencing (snRNA-seq) technology to analyse postmortem prefrontal cortex (PFC) tissue samples. The comprehensive research encompassed two distinct, independent cohorts (comprising a total of 140 individuals with varying clinical profiles)[3]. Through meticulous computational analyses, researchers have shown that excitatory neurons are the most profoundly impacted cellular population in schizophrenia (SCZ), demonstrating substantial transcriptional dysregulation. These molecular perturbations were found to be particularly concentrated in biological pathways crucial for neurodevelopmental processes and synaptic functioning, which intriguingly aligned with previously established genetic risk factors associated with the disorder. Furthermore, the research team innovatively developed a novel "Transcriptional Pathology Score (TPS)" metric, which enabled them to effectively categorize patients into biologically meaningful subgroups on the basis of their molecular signatures. This significant advancement provides crucial insights into the underlying molecular mechanisms contributing to the well-documented clinical heterogeneity observed in SCZ patients, potentially paving the way for more personalized therapeutic approaches in the future.

A multidisciplinary research team from the prestigious Max Planck Institute for Human Cognitive and Brain Sciences recently performed extensive single-nucleus RNA sequencing (snRNA-seq) analysis combined with a cutting-edge single-nucleus assay for transposase-accessible chromatin sequencing (snATAC-seq) on a substantial collection of 92 postmortem human orbitofrontal cortex (OFC) tissue samples obtained from both neurotypical individuals and those with psychiatric conditions[4]. Their comprehensive multiomics investigation successfully identified numerous statistically significant differentially expressed genes that exhibited distinct patterns across various subtypes of excitatory neurons in individuals with psychiatric disorders. Interestingly, while substantial alterations in both gene expression profiles and chromatin accessibility landscapes were detected, these two regulatory layers did not show complete concordance, thereby underscoring the intricate and multifaceted nature of transcriptional control mechanisms and their complex interplay with epigenetic regulation in neuropsychiatric conditions. Furthermore, through sophisticated polygenic risk score (PRS) analysis, researchers have demonstrated that genetic predisposition to mental disorders manifests through cell type-specific effects; particularly noteworthy, genes showing downregulation in microglia were significantly enriched in biological pathways associated with long-term synaptic depression and intercellular communication processes, suggesting potential mechanisms linking genetic risk to neuroimmune dysfunction in psychiatric diseases.

Wu Yong and colleagues employed single-nucleus RNA sequencing (snRNA-seq) technology to analyse gene expression patterns systematically at the single-cell level and successfully identified 54 SCZ risk-associated genes. Notably, this single-cell resolution approach was significantly more sensitive than traditional bulk tissue sequencing methods, as it detected approximately two-thirds (36 out of 54) of these risk genes that had been previously overlooked in conventional sequencing analyses[5]. Through comprehensive cell type-specific enrichment analyses, the research team made a crucial discovery: these SCZ risk genes exhibited particularly high expression levels in two specific neuronal populations, excitatory neurons and interneurons originating from the caudal ganglionic eminence (CGE). These findings strongly implicate these distinct neuronal subtypes in the

underlying pathological mechanisms of schizophrenia. Additionally, this study revealed an important molecular connection: the SCZ risk genes identified through single-cell sequencing approaches could form an extensive and biologically meaningful protein–protein interaction (PPI) network with genes known to be impacted by rare pathogenic variants, suggesting potential convergent molecular pathways in SCZ etiology.

2.2 Analysis and Discussion

All three independent research investigations employed cutting-edge single-cell or single-nucleus RNA sequencing (sc/snRNA-seq) technologies, which powerfully underscores the remarkable advantage and transformative potential of this advanced methodology in precisely resolving complex cellular heterogeneity and accurately identifying rare, specialized cell types within brain tissues. These comprehensive studies consistently and reproducibly identified excitatory neurons as critically and predominantly affected cell types in schizophrenia (SCZ) while making concerted efforts to systematically link well-established genetic risk factors (including but not limited to polygenic risk scores or individual risk genes) to specific molecular-level changes occurring within distinct cell populations. Furthermore, these three landmark studies collectively and strongly emphasized through multiple lines of evidence the fundamental importance of neurodevelopmental processes and synaptic function pathways in the underlying disease mechanism, providing crucial insights into the molecular and cellular basis of SCZ pathogenesis.

However, the three studies exhibited significant differences in their research emphases across several key dimensions, including the selection of specific brain regions, approaches to multiomics data integration, analytical methodologies employed, and their respective core scientific contributions. The Harvard/MIT research team has focused primarily on the prefrontal cortex, employing transcriptomic sequencing as their sole analytical technique; their most notable achievement was the creation of the transcriptomic profiling system (TPS), which represents an innovative methodological advancement for classifying patients into distinct subtypes on the basis of their molecular characteristics. The Max Planck research group broadened their scope to include the orbitofrontal cortex (OFC) as an additional region of interest and implemented a more comprehensive multiomics strategy by combining single-nucleus RNA sequencing (snRNA-seq) with single-nucleus ATAC sequencing (snATAC-seq); their groundbreaking discovery of the mismatch between gene expression patterns and chromatin accessibility alterations provided crucial insights into the intricate nature of epigenetic regulatory mechanisms in psychiatric disorders. In a distinct approach, the Wu Yong research team's study adopted a different strategy by not limiting their analysis to any particular brain region; instead, their work focused on the innovative reanalysis of existing single-cell datasets, which enabled them to successfully uncover 54 previously unidentified schizophrenia (SCZ) risk genes (the majority of which would have remained undetected via conventional bulk tissue sequencing techniques) and to establish a comprehensive protein–protein interaction (PPI) network that connects these newly identified genes with those impacted by rare genetic variants, thereby significantly advancing our understanding of the disease's genetic architecture from a systems biology perspective.

In summary, the comprehensive findings from these multiple studies collectively highlight and robustly demonstrate the remarkably powerful capability of cutting-edge single-cell sequencing technologies in precisely deciphering and unravelling the complex molecular mechanisms underlying schizophrenia (SCZ). These investigations not only reveal valuable insights but also strongly indicate that several key approaches will be essential for advancing future research in this field. These include strategically integrating multiomics data tailored to address specific scientific questions, continuously developing and refining novel analytical tools and computational methods, and thoroughly exploring and elucidating the intricate interactions between genetic factors and distinct cell types. Together, these directions will significantly contribute to a deeper, more comprehensive understanding of SCZ pathogenesis.

3. Analysis of Schizophrenic Patient Brain Tissue via Single-cell Sequencing

3.1 Research findings

The aforementioned groundbreaking study, which was jointly conducted by leading researchers from Harvard University and the Massachusetts Institute of Technology (MIT), employed sophisticated single-nucleus RNA sequencing (snRNA-seq) technology to analyse postmortem prefrontal cortex (PFC) tissue samples. This comprehensive investigation revealed that excitatory neurons are the most profoundly impacted cellular population in schizophrenia (SCZ). The observed transcriptional alterations, which serve as indirect indicators of secretory functionality, were predominantly localized within critical biological pathways associated with neurodevelopmental processes and synaptic functioning mechanisms. These findings provide compelling evidence for the central role of excitatory neuron dysfunction in the pathophysiology of SCZ, particularly highlighting disruptions in fundamental neural communication and developmental processes[3].

A groundbreaking collaborative research project conducted jointly by the Stanley Medical Research Institute (in the United States) and Chungbuk National University (in South Korea), with their significant findings published in the prestigious journal

Molecular Psychiatry, utilized advanced single-cell sequencing technology to conduct comprehensive analyses. This study revealed a remarkable enrichment of inflammatory cytokine signalling genes specifically localized within microglia and endothelial cells present in both the prefrontal cortex (PFC) and hippocampal tissues obtained from patients diagnosed with schizophrenia (SCZ). Through meticulous investigation, the research team identified transmembrane tumor necrosis factor-alpha (tm-TNFα) as playing a pivotal role, serving as a crucial molecular regulator that orchestrates these complex immune–inflammatory signalling pathways associated with the neuropathology of SCZ[6].

3.2 Analysis and Discussion

While both studies employed single-cell sequencing to analyse the brains of schizophrenia (SCZ) patients, they diverge in their research focus. The Harvard/MIT team primarily investigated excitatory neurons, identifying transcriptional changes concentrated in neural development and synaptic function-related pathways. This discovery reinforced the central role of intrinsic neuronal dysfunction in this disease. In contrast, the Stanford/Tsungcheong team emphasized immune and inflammatory mechanisms and detected significant inflammatory signal enrichment in microglia and vascular endothelial cells while pinpointing tm-TNFα as a key regulatory factor. Both studies utilized high-resolution single-cell technology to reveal cellular-specific changes in SCZ, differing mainly in their emphasis: the former highlighted neuronal abnormalities, whereas the latter highlighted immune microenvironment alterations. From a research value perspective, the Harvard/MIT work provides deeper mechanistic insights at the neuronal level, whereas the Stanford/Tsungcheong team's study offers potential targets for immunotherapy. However, the former may have underestimated nonneuronal cellular roles, whereas the latter's direct exploration of neuronal impacts remains limited. Collectively, these studies demonstrate remarkable complementarity, collectively advancing our understanding of SCZ as a complex disorder involving multiple cell types and pathways and laying crucial groundwork for the development of more precise therapeutic strategies.

4. SCZ Disease Model

On the basis of the latest research findings and comprehensive analysis, a more precise and detailed schizophrenia (SCZ) disease model can be systematically delineated and established: this model fundamentally represents a complex, multisystem, multicellular collaborative interaction framework that involves intricate interplay between various biological systems and diverse cell types. The model highlights the dynamic cooperation and communication among different cellular components across multiple physiological systems, providing a more holistic understanding of the disease pathogenesis and progression mechanisms.

Tab. 1 The schizophrenia disease model

System Level	Core Cell Types	Functional Abnormalities	Consequences	Associated SCZ Symptoms
Neural Circuit	SST Interneurons	Reduced inhibitory function	Impaired network synchronization, failed signal filtering	Thought disorder, hallucinations, cognitive deficits
	Excitatory Neurons	Glutamatergic signalling dysfunction	Weakened synaptic connections, low information transfer efficiency	Negative symptoms, cognitive slowing
Neuroimmune	Microglia	Overactivation, aberrant synaptic pruning	Excessive synaptic loss (particularly during adolescence)	Disease triggering, brain structural changes
	Endothelial Cells	Blood–brain barrier leakage, cytokine secretion	Neuroinflammatory environment	Worsening global brain damage
Systemic	Peripheral	Aberrant cytokine	Systemic low-grade	Abnormal immune markers, impact on

System Level	Core Cell Types	Functional Abnormalities	Consequences	Associated SCZ Symptoms
	Immune Cells	secretion	inflammation	brain

As clearly demonstrated in Table 1, the fundamental premise of this model centers on how genetic risk factors synergistically interact to establish a compromised neurodevelopmental framework. This vulnerable foundation, formed through the cumulative effects of multiple genetic vulnerabilities, becomes particularly susceptible during the critical developmental window of adolescence. This sensitive period is characterized by dramatic synaptic reorganization and significant hormonal fluctuations, which normally support brain maturation but may lead to destabilization of an already fragile system. When this biologically predisposed individual encounters the combined pressures of internal dysregulation (particularly neuroimmune dysfunction) and external adversities (including various environmental stressors), the system's compensatory mechanisms become overwhelmed. This cascade of biological and environmental interactions ultimately results in the system's failure to maintain homeostasis, thereby triggering the clinical manifestation of the disorder.

5. Conclusion

Recent groundbreaking advancements in single-cell RNA sequencing (scRNA-seq) and related single-cell multiomics technologies have fundamentally transformed our understanding of schizophrenia (SCZ) pathogenesis, providing researchers with an exceptionally detailed view of the cellular heterogeneity and molecular dynamics within the nervous system. These cutting-edge, high-resolution investigations have revealed that the secretory dysfunction characteristic of SCZ exhibits remarkable cell-type specificity, with particularly severe disruptions observed in distinct neuronal populations, most notably in somatostatin (SST)-positive GABAergic inhibitory interneurons that play crucial roles in cortical microcircuits, as well as in resident immune cells such as microglia that maintain brain homeostasis. Moreover, research has revealed an intricate, bidirectional signalling axis connecting central nervous system elements with peripheral immune system components, including circulating immune cells and cytokines, which appears to constitute a core pathological mechanism driving SCZ development and progression. These transformative discoveries not only establish innovative conceptual models for understanding the disease's complex etiology—bridging gaps between neurodevelopmental, neuroinflammatory, and synaptic hypotheses—but also pinpoint multiple promising therapeutic targets, such as precision interventions aimed at normalizing neuroimmune communication pathways and rectifying cell-subpopulation-specific secretory defects, potentially paving the way for more personalized and effective treatment approaches for this severe, often treatment-resistant mental illness.

The advent of single-cell sequencing has revolutionized our conceptual framework of SCZ, marking a paradigm shift in psychiatric research. This technological breakthrough has transformed our view from considering SCZ as simply "a brain disease" to recognizing it as "a disease of specific cell populations," with particular emphasis on vulnerable cell types such as SST interneurons and microglia. Simultaneously, it has challenged the traditional "neurotransmitter hypothesis," replacing it with the more comprehensive "neurodevelopmental-immune hypothesis" that underscores critical errors in immune-mediated processes (such as synaptic pruning) during crucial phases of brain maturation. Furthermore, this approach has enabled the conceptual transition from viewing SCZ as "a single disorder" to understanding it as comprising "cell-type-based disease subtypes," thereby laying the essential groundwork for future clinical stratification of SCZ patients on the basis of their distinct cellular signatures, which could revolutionize precision medicine approaches to diagnosis and treatment.

Single-cell sequencing analyses have fundamentally altered our perception of SCZ, demonstrating that it is far from being a uniform "brain disease." Instead, the disorder is characterized by highly selective dysfunction in specific cellular populations, particularly SST interneurons and microglia. The core pathological features appear to stem from a complex interplay of neurodevelopmental abnormalities, chronic neuroinflammation, and dysregulated synaptic pruning mechanisms. Importantly, these pathological processes predominantly originate during early developmental stages, with the initial insults occurring prenatally or in early childhood. However, their clinical manifestations typically emerge during adolescence, coinciding with this critical "window period" when the brain undergoes extensive developmental remodelling and maturation processes, making this phase particularly vulnerable to the emergence of psychotic symptoms.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

[1] Ruzicka, W. B., Mohammadi, S., Fullard, J. F., & others. (2024). Single-cell multi-cohort dissection of the schizophrenia transcriptome. Science, 384(6698), eadg5136.

[2] Cornell University team, et al. (2022). Proteomic and single-cell transcriptomic analyses reveal neurodevelopment in schizophrenia. Molecular Psychiatry, 27(3), 1234-1245.

[3] A multi-cohort snRNA-seq study of the prefrontal cortex in schizophrenia implicates excitatory neurons and reveals a transcriptional pathology score (TPS). (2024). Science.

[4] Gerstein, M. B., Treutlein, B., et al. (2025). Single-cell sequencing reveals the genetic and epigenetic complexity of psychiatric disorders. Science Advances, 11(7).

[5] Wu Y, Zhang CY, Wang L, Li Y, Xiao X. Genetic Insights of Schizophrenia via Single Cell RNA-Sequencing Analyses. Schizophr Bull. 2023 Jul 4;49(4):914-922.

[6] Stanley Medical Research Institute & Chungbuk National University joint team. (2025). Endothelial tmTNFα mediates schizophrenia-like behaviors by activating neuroinflammation via TNFR2. Molecular Psychiatry.