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Single-Cell Multiomics in Neurological Disorders: Transforming Disease Mechanisms and Precision Medicine

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Mini Review

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Abstract

Neurological disorders represent a major global health challenge owing to their increasing prevalence, clinical heterogeneity, and limited disease-modifying therapies. Traditional molecular profiling techniques have significantly advanced our understanding of neurological diseases; however, they often fail to capture the cellular diversity and dynamic molecular interactions that characterize the central nervous system. Recent advances in single-cell multiomics have enabled simultaneous analysis of genomic, transcriptomic, epigenomic, proteomic, and spatial molecular information at single-cell resolution, providing unprecedented insights into cellular heterogeneity, intercellular communication, and disease-associated molecular pathways. These technologies have transformed the investigation of neurodegenerative, neuroinflammatory, cerebrovascular, and neuro-oncological disorders by identifying novel cell populations, disease-specific biomarkers, and potential therapeutic targets. Furthermore, integrating artificial intelligence with single-cell multiomics is facilitating precision neurology through improved disease classification, biomarker discovery, and personalized therapeutic strategies. Despite these advances, challenges related to data integration, computational complexity, high costs, and clinical translation continue to limit widespread implementation. This mini review summarizes recent developments in single-cell multiomics, highlights its applications across major neurological disorders, discusses current limitations, and explores future opportunities for translating these technologies into precision neurological care.

Keywords: Single-cell multiomics; Precision neurology; Neurodegenerative diseases; Spatial transcriptomics; Single-cell RNA sequencing; Multiomics integration; Biomarkers; Artificial intelligence; Neuroinflammation; Precision medicine

Abbreviations

AD: Alzheimer's Disease; PD: Parkinson's Disease; MS: Multiple Sclerosis; ALS: Amyotrophic Lateral Sclerosis; CNS: Central Nervous System; AI: Artificial Intelligence.

Introduction

Neurological disorders account for one of the leading causes of disability and mortality worldwide, affecting billions of individuals and imposing an enormous socioeconomic burden on healthcare systems. Diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), stroke, and primary brain tumors exhibit remarkable clinical and molecular heterogeneity, making early diagnosis and effective treatment particularly challenging. Although advances in neuroimaging, molecular biology, and genomic technologies have substantially improved disease characterization, conventional bulk sequencing approaches average molecular signals across heterogeneous cell populations and therefore fail to reveal the cellular complexity of the central nervous system (CNS). Consequently, important disease-driving cellular subpopulations and molecular mechanisms may remain undetected, limiting the discovery of reliable biomarkers and targeted therapeutic strategies [1,2].

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The emergence of single-cell sequencing technologies has revolutionized neuroscience by enabling high-resolution characterization of individual cells within healthy and diseased brain tissues. Single-cell RNA sequencing (scRNA-seq) was initially developed to investigate transcriptomic diversity, revealing previously unrecognized neuronal and glial cell subtypes and their functional states. More recently, technological innovations have expanded beyond transcriptomics to include simultaneous profiling of chromatin accessibility, DNA methylation, protein expression, immune receptor repertoires, metabolomic signatures, and spatial transcriptomics. Collectively, these complementary approaches are referred to as single-cell multiomics, providing a comprehensive understanding of cellular identity, molecular regulation, and cell-to-cell interactions within complex neurological microenvironments [3,4].

Single-cell multiomics has significantly advanced the understanding of disease mechanisms across a broad spectrum of neurological disorders. In Alzheimer's disease, these technologies have identified disease-associated microglia, astrocyte subpopulations, and neuronal vulnerability signatures associated with amyloid-β accumulation and tau pathology. Similarly, in Parkinson's disease, single-cell analyses have uncovered dopaminergic neuronal heterogeneity, mitochondrial dysfunction, and neuroimmune alterations that contribute to disease progression. In multiple sclerosis, integrated single-cell transcriptomic and epigenomic profiling has improved our understanding of immune cell infiltration, demyelination, and remyelination processes, thereby identifying novel therapeutic targets [5,7].

Another major advantage of single-cell multiomics is its ability to facilitate precision neurology by integrating molecular information from individual patients. Combining multiomics datasets with artificial intelligence (AI), machine learning algorithms, and advanced computational biology enables the identification of predictive biomarkers, patient-specific disease trajectories, and individualized therapeutic responses. Such approaches have the potential to transform neurological care by moving beyond conventional symptom-based diagnosis toward mechanism-based precision medicine. Furthermore, spatial multiomics technologies preserve tissue architecture while simultaneously mapping molecular signatures, thereby providing valuable insights into cellular communication networks within the brain and spinal cord [2].

Despite remarkable technological progress, several challenges remain before single-cell multiomics can be routinely implemented in clinical neurology. High experimental costs, standardized sample preparation, computational infrastructure, data integration across multiple omics platforms, reproducibility, and ethical considerations regarding large-scale molecular datasets continue to limit widespread clinical translation. Nevertheless, ongoing advances in sequencing technologies, bioinformatics, cloud computing, and AI-driven analytical pipelines are expected to overcome many of these barriers over the coming years [4].

This mini review discusses recent advances in single-cell multiomics technologies, summarizes their applications in major neurological disorders, highlights current limitations, and explores future opportunities for integrating these approaches into precision neurology and personalized patient care.

Technologies and Methodological Advances

The rapid evolution of single-cell technologies has transformed molecular neuroscience by enabling the simultaneous characterization of multiple biological layers within individual cells. While single-cell RNA sequencing (scRNA-seq) remains the most widely adopted platform for investigating cellular transcriptomes, recent technological innovations have expanded analytical capabilities to include chromatin accessibility (scATAC-seq), DNA methylation profiling, single-cell proteomics, metabolomics, immune receptor sequencing, and spatial transcriptomics.

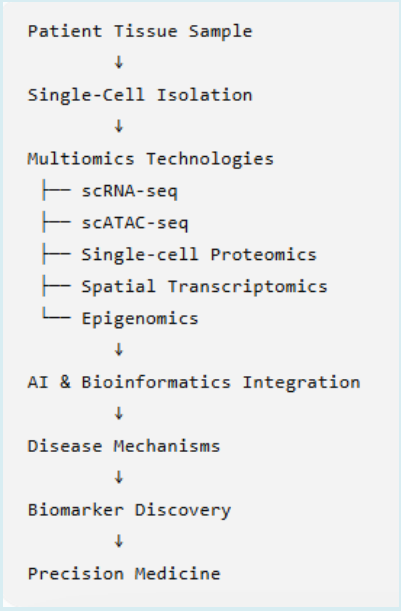

Figure 1: Overview of Single-Cell Multiomics Workflow in Neurological Research.

Integration of these complementary datasets, collectively referred to as single-cell multiomics, enables comprehensive characterization of cellular identity, regulatory networks, and

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functional states that cannot be achieved using individual omics technologies alone. These approaches have become particularly valuable for studying the remarkable cellular heterogeneity of the human central nervous system (CNS), where neurons, astrocytes, oligodendrocytes, microglia, endothelial cells, and infiltrating immune cells dynamically interact during health and disease (Figure 1).

One of the most significant methodological advances has been the development of multimodal sequencing platforms capable of simultaneously measuring gene expression and chromatin accessibility within the same cell. These technologies allow researchers to directly associate transcriptional activity with epigenetic regulation, thereby improving our understanding of cell differentiation, lineage commitment, and disease-associated molecular alterations. Similarly, combined transcriptomic and proteomic platforms provide more accurate characterization of cellular phenotypes because messenger RNA abundance does not always correlate with protein expression. Spatial transcriptomics further complements these approaches by preserving tissue architecture while mapping molecular signatures to their anatomical locations, allowing investigators to examine how pathological changes evolve within distinct brain regions and cellular niches [1,2].

Technology	Purpose	Neurological Application
scRNA-seq	Gene expression profiling	Cell-type identification
scATAC-seq	Chromatin accessibility	Epigenetic regulation
Spatial transcriptomics	Spatial gene expression	Tissue architecture
Single-cell proteomics	Protein expression	Biomarker discovery

Table 1: Major Single-Cell Multiomics Technologies.

Computational biology has become an indispensable component of single-cell multiomics research. Machine learning algorithms and artificial intelligence (AI) are increasingly used to integrate large-scale transcriptomic, epigenomic, proteomic, and spatial datasets, identify previously unrecognized cellular populations, reconstruct developmental trajectories, and infer intercellular communication networks. These computational advances have substantially improved the reproducibility and biological interpretation of complex datasets while facilitating biomarker discovery and therapeutic target identification. However, challenges remain regarding data standardization, batch-effect correction, computational scalability, and harmonization of datasets generated using different sequencing platforms. Continued improvements in bioinformatics pipelines and cloud-based analytical frameworks are expected to accelerate the clinical translation of single-cell multiomics in neurology (Table 1).

Applications in Alzheimer's Disease

Alzheimer's disease (AD) is characterized by progressive cognitive decline associated with amyloid-β deposition, tau neurofibrillary tangles, synaptic dysfunction, and neuronal loss. Although conventional genomic and transcriptomic studies have identified numerous susceptibility genes, bulk tissue analyses often obscure disease-associated molecular alterations occurring within specific cell populations. Single-cell multiomics has overcome this limitation by revealing remarkable cellular diversity and identifying vulnerable neuronal subtypes that undergo selective degeneration during disease progression. Recent large-scale single-cell atlases have demonstrated that excitatory neurons within particular cortical and hippocampal regions exhibit distinct transcriptional signatures associated with increased susceptibility to AD pathology. These discoveries provide important insights into regional vulnerability and disease progression.

Microglia have emerged as one of the most extensively investigated cell populations using single-cell approaches. Disease-associated microglia (DAM) display unique transcriptional programs characterized by activation of inflammatory signaling pathways, enhanced phagocytic activity, lipid metabolism alterations, and increased expression of risk genes such as TREM2, APOE, and TYROBP. These findings suggest that microglial activation is not merely a secondary response to amyloid accumulation but may actively influence neurodegeneration and disease progression. Similarly, astrocytes exhibit multiple reactive phenotypes that contribute to neuroinflammation, synaptic dysfunction, metabolic disturbances, and blood-brain barrier alterations. Single-cell multiomics has therefore fundamentally changed the understanding of glial biology in Alzheimer's disease by demonstrating substantial functional heterogeneity among glial populations [1].

Beyond identifying disease mechanisms, single-cell multiomics is facilitating biomarker discovery and precision medicine. Integration of transcriptomic, epigenomic, and spatial molecular information enables researchers to identify molecular signatures associated with disease stage, cognitive decline, and therapeutic response. Artificial intelligence-assisted analysis of these multidimensional datasets is expected to improve patient stratification for clinical trials and support individualized therapeutic interventions targeting specific cellular pathways rather than generalized pathological processes. Although further validation in large patient cohorts remains necessary, these technologies represent a major step

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toward precision neurology in Alzheimer's disease.

Applications in Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily characterized by degeneration of dopaminergic neurons within the substantia nigra pars compacta and widespread abnormalities involving mitochondrial function, α-synuclein aggregation, oxidative stress, and neuroinflammation. Single-cell multiomics has substantially expanded current understanding of PD by demonstrating that dopaminergic neurons are not a homogeneous population but instead comprise multiple molecularly distinct subtypes exhibiting different levels of vulnerability to neurodegeneration. Identification of these selectively vulnerable neuronal populations provides important clues regarding disease initiation and progression [3].

Recent single-cell transcriptomic and epigenomic studies have further demonstrated significant alterations in glial cells during Parkinson's disease. Activated microglia exhibit increased expression of inflammatory mediators, whereas astrocytes undergo metabolic and transcriptional remodeling that influences neuronal survival. Oligodendrocytes and endothelial cells also demonstrate disease-associated molecular changes, suggesting that Parkinson's disease involves complex multicellular interactions rather than isolated neuronal degeneration. Integration of multiple omics layers has enabled reconstruction of cellular communication networks responsible for chronic neuroinflammation and progressive neuronal loss [1,3].

Another promising application of single-cell multiomics in Parkinson's disease involves biomarker discovery and therapeutic target identification. Combined transcriptomic and epigenomic profiling has revealed dysregulated pathways involving mitochondrial quality control, lysosomal degradation, protein homeostasis, and immune signaling. These molecular signatures may facilitate earlier diagnosis before substantial neuronal loss occurs while simultaneously identifying patient-specific therapeutic targets. Furthermore, integrating single-cell multiomics with artificial intelligence is expected to improve disease classification, predict progression, and optimize individualized treatment strategies. As sequencing technologies become increasingly accessible and computational methods continue to mature, single-cell multiomics is likely to become an integral component of precision medicine approaches for Parkinson's disease [5].

Applications in Multiple Sclerosis

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disorder of the central nervous system characterized by inflammatory lesions, axonal degeneration, and progressive neurological disability. Although conventional immunological studies have identified several immune pathways involved in disease progression, they have been unable to fully explain the remarkable cellular heterogeneity observed among patients. Single-cell multiomics has emerged as a powerful approach for dissecting the complex immune landscape of MS by simultaneously characterizing gene expression, chromatin accessibility, and immune-cell phenotypes at single-cell resolution. These studies have demonstrated that peripheral immune cells, resident microglia, astrocytes, oligodendrocytes, and infiltrating macrophages contribute differently to disease initiation and progression, revealing previously unrecognized cellular interactions within active lesions [1,4].

Recent single-cell transcriptomic analyses have identified multiple inflammatory T-cell and B-cell subsets with distinct pathogenic roles in MS. Likewise, disease-associated microglia exhibit transcriptional programs linked to antigen presentation, cytokine production, and oxidative stress, whereas oligodendrocyte precursor cells demonstrate variable capacities for remyelination. Integration of transcriptomic and epigenomic datasets has further revealed regulatory mechanisms controlling immune activation and myelin repair, providing potential therapeutic targets for promoting neuroprotection and remyelination.

Single-cell multiomics has also contributed to precision medicine by identifying biomarkers associated with treatment response. Molecular signatures obtained from immune cells before therapy have shown promise in predicting responsiveness to disease-modifying agents, thereby supporting individualized treatment strategies. As longitudinal single-cell studies become more common, these approaches may facilitate disease monitoring and early identification of patients at risk for rapid progression [6].

Applications in Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disorder characterized by degeneration of upper and lower motor neurons, ultimately leading to muscle weakness, respiratory failure, and death. The underlying mechanisms involve genetic susceptibility, RNA metabolism abnormalities, mitochondrial dysfunction, protein aggregation, excitotoxicity, and neuroinflammation. Single-cell multiomics has significantly expanded current understanding of ALS by revealing cell-specific molecular alterations that are masked in conventional bulk tissue analyses [1,5].

Recent studies have demonstrated considerable heterogeneity among motor neurons, identifying selectively

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vulnerable neuronal populations with dysregulated RNA processing, impaired energy metabolism, and defective proteostasis. Furthermore, reactive astrocytes and activated microglia display distinct inflammatory phenotypes that actively contribute to neuronal degeneration through cytokine secretion, oxidative stress, and impaired neuronal support. Integration of transcriptomic, epigenomic, and spatial molecular profiling has enabled reconstruction of disease-associated cellular communication networks, highlighting the importance of non-neuronal cells in ALS pathogenesis.

The application of single-cell multiomics has also accelerated biomarker discovery by identifying molecular signatures associated with disease progression and survival. These findings may facilitate earlier diagnosis and improve patient selection for clinical trials investigating targeted therapeutic interventions.

Applications in Stroke

Stroke remains one of the leading causes of mortality and long-term disability worldwide. Despite substantial improvements in acute management, the molecular mechanisms governing neuronal injury, neuroinflammation, vascular remodeling, and functional recovery remain incompletely understood. Single-cell multiomics has provided unprecedented insights into the dynamic cellular responses that occur following cerebral ischemia by characterizing neuronal, glial, endothelial, and immune-cell populations throughout different stages of injury and recovery.

Single-cell sequencing studies have demonstrated that ischemic stroke triggers rapid activation of microglia, infiltration of peripheral immune cells, astrocyte remodeling, endothelial dysfunction, and alterations in oligodendrocyte precursor cells. These molecular responses vary considerably according to the severity of ischemia, anatomical location, and recovery stage. Spatial transcriptomics has further enabled visualization of cellular communication within the ischemic penumbra, identifying signaling pathways that regulate neurovascular remodeling and tissue repair.

Combining multiomics data with artificial intelligence has improved identification of prognostic biomarkers associated with infarct size, neurological recovery, and post-stroke complications. These approaches may facilitate patient stratification and guide personalized rehabilitation strategies in future clinical practice.

Applications in Brain Tumors

Primary brain tumors, particularly glioblastoma, exhibit remarkable cellular diversity that contributes to therapeutic resistance and poor clinical outcomes. Traditional genomic studies have provided valuable insights into tumor biology but frequently overlook intratumoral heterogeneity. Single-cell multiomics has transformed neuro-oncology by enabling comprehensive characterization of malignant cells together with immune, vascular, and stromal components within the tumor microenvironment [7].

Recent investigations have demonstrated that glioblastoma consists of multiple transcriptionally distinct tumor cell states capable of dynamic interconversion during disease progression and treatment. Single-cell epigenomic analyses have further identified regulatory programs responsible for tumor plasticity, invasion, and resistance to chemotherapy and radiotherapy. In parallel, immune profiling has revealed complex interactions between tumor-associated macrophages, microglia, T lymphocytes, and malignant cells that influence immune suppression and treatment response.

These findings provide opportunities for identifying patient-specific therapeutic targets and optimizing precision oncology strategies. Integration of spatial transcriptomics with single-cell multiomics is expected to further improve understanding of tumor architecture and therapeutic resistance (Figure 2 & Table 2).



Figure 2: Applications of Single-Cell Multiomics in Neurological Disorders.

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Disorder	Key Findings	Clinical Significance
Alzheimer's disease	Disease-associated microglia	Early diagnosis
Parkinson's disease	Neuronal heterogeneity	Targeted therapy
Multiple sclerosis	Immune-cell diversity	Personalized treatment
ALS	Cell-specific degeneration	Biomarker discovery
Stroke	Neurovascular remodeling	Prognosis
Glioblastoma	Tumor heterogeneity	Precision oncology

Table 2: Clinical Applications Across Neurological Disorders.

Challenges and Future Perspectives

Despite its transformative potential, several barriers currently limit the routine clinical implementation of single-cell multiomics in neurology. One major challenge is the substantial computational complexity associated with integrating transcriptomic, epigenomic, proteomic, metabolomic, and spatial datasets generated from thousands to millions of individual cells. Standardization of analytical pipelines, batch-effect correction, reproducibility across laboratories, and harmonization of sequencing platforms remain active areas of methodological development [6,7].

Another important limitation is the high cost of sequencing technologies and specialized computational infrastructure, which restricts their widespread adoption in routine clinical practice. Sample preparation, tissue preservation, and technical variability may also influence data quality and biological interpretation. Furthermore, ethical issues concerning genomic privacy, secure data sharing, informed consent, and responsible application of artificial intelligence require careful consideration before large-scale implementation [5.6].

Future research should prioritize longitudinal single-cell studies that monitor disease progression over time rather than relying solely on cross-sectional analyses. Integration of single-cell multiomics with digital pathology, advanced neuroimaging, wearable health technologies, and artificial intelligence will likely enable comprehensive patient-specific disease models capable of predicting disease progression and therapeutic response. Cloud-based analytical platforms and increasingly accessible sequencing technologies are expected to reduce computational barriers while facilitating multicenter collaborations and clinical translation.

Ultimately, single-cell multiomics has the potential to redefine precision neurology by enabling mechanism-based diagnosis, individualized therapeutic selection, early biomarker discovery, and continuous molecular monitoring. Continued interdisciplinary collaboration among neuroscientists, clinicians, computational biologists, engineers, and bioinformaticians will be essential to translating these technological advances into improved patient outcomes.

Conclusion

Single-cell multiomics has emerged as one of the most transformative technological advances in modern neuroscience, providing unprecedented opportunities to investigate the molecular complexity of neurological disorders at single-cell resolution. Unlike conventional bulk sequencing approaches, multiomic technologies simultaneously characterize transcriptomic, epigenomic, proteomic, metabolomic, and spatial information from individual cells, thereby revealing cellular heterogeneity, regulatory networks, and intercellular communication that drive disease pathogenesis. This comprehensive molecular perspective has substantially improved our understanding of Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, stroke, and primary brain tumors by identifying disease-associated cellular populations, novel biomarkers, and potential therapeutic targets.

The integration of artificial intelligence and advanced computational biology with single-cell multiomics is accelerating biomarker discovery, patient stratification, and precision medicine. These technologies have the potential to support earlier diagnosis, improve prognostic assessment, predict therapeutic response, and facilitate personalized treatment strategies based on patient-specific molecular profiles. Furthermore, combining single-cell sequencing with spatial transcriptomics, digital pathology, neuroimaging, and wearable health technologies may provide a comprehensive framework for individualized neurological care.

Despite these remarkable advances, important challenges remain before routine clinical implementation becomes feasible. High sequencing costs, complex bioinformatic analyses, limited standardization across platforms, technical variability, and concerns regarding data privacy and ethical governance continue to impede widespread adoption. Addressing these barriers will require multidisciplinary collaboration among neurologists, molecular biologists, bioinformaticians, computational scientists, and regulatory authorities to establish standardized analytical pipelines and clinically validated biomarkers.

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Looking ahead, continuous improvements in sequencing technologies, artificial intelligence, cloud computing, and multimodal data integration are expected to further enhance the clinical utility of single-cell multiomics. Future large-scale longitudinal studies and multicenter collaborative initiatives will be essential for translating experimental discoveries into routine neurological practice. Ultimately, single-cell multiomics represents a major step toward precision neurology, offering new opportunities to improve disease diagnosis, therapeutic decision-making, and long-term patient outcomes through individualized molecular medicine.

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