International Journal of Biological and Pharmaceutical Sciences Archive

ISSN: 0799-6616 (Online)

Journal homepage: https://ijbpsa.com/

(REVIEW ARTICLE)

Spatial transcriptomics in Alzheimer's disease: Mapping cellular dysregulation in the brain microenvironment

Tobiloba Philip Olatokun [1, *], James Busayo Agboola [2], Buniechukwuenu Emmanuel Mbamalu [3], Nyerovwo Charity Okei [4], David Oluwafemi Ibikunle [5], Lessly Kyei Poku [6] and Osahenrumwen Edobor [7]

[1] *Department of Internal Medicine (Consulting group), Obafemi Awolowo University Health Center, Ile-Ife, Nigeria.*
[2] *Department of Biochemistry and Molecular Biology, Obafemi Awolowo University, Ile-Ife, Nigeria.*
[3] *School of Medicine, St George's University, St. George's, Grenada.*
[4] *Department of Biological Sciences, University of Camerino, Italy.*
[5] *Department of Medicine and Surgery, Obafemi Awolowo University, Ife., Nigeria.*
[6] *Department of Department of Community Medicine, College of Health and Well-Being, Kintampo, Ghana.*
[7] *Department of Pharmacy, University of Benin, Benin city, Nigeria.*

International Journal of Biological and Pharmaceutical Sciences Archive, 2025, 10(01), 121-140

Publication history: Received on 24 June 2025; revised on 05 August; accepted on 08 August 2025

Article DOI: https://doi.org/10.53771/ijbpsa.2025.10.1.0064

Abstract

Alzheimer's disease (AD), a leading cause of dementia, imposes a profound global burden, characterized by amyloid-β plaques, tau tangles, and progressive cognitive decline. Spatial transcriptomics (ST) has emerged as a transformative tool, mapping the brain's complex microenvironment with unprecedented precision to reveal molecular underpinnings of AD pathology. This review explores ST's role in dissecting the interactions of neurons, microglia, astrocytes, oligodendrocytes, and the neurovascular unit, uncovering spatially restricted dysregulation in regions like the hippocampus and cortex. By resolving plaque-induced inflammatory genes, synaptic loss markers, and vascular dysfunction, ST illuminates AD's cellular heterogeneity across early/late stages and genetic/sporadic subtypes, offering a molecular blueprint for precision medicine. Open-access datasets, including GEO and comprehensive brain atlases, have accelerated these discoveries, fostering collaborative research into AD's microenvironmental dynamics.ST's clinical promise lies in its ability to inform therapeutic and diagnostic innovations. Biomarkers like microglial TREM2 and endothelial LRP1, identified through ST, guide patient stratification for anti-amyloid therapies and emerging microglial or vascular-targeted interventions, while enabling early detection through subtle entorhinal cortex changes. Despite challenges—resolution limits, data complexity, high costs, and ethical concerns—future directions, including AI-driven analysis, multi-omics integration, and novel platforms like STORM-seq, promise to overcome these hurdles. By bridging basic research and clinical practice, ST holds the potential to redefine AD management, offering hope for earlier diagnostics and personalized therapies to mitigate this devastating disease's impact.

Keywords: Spatial Transcriptomics; Alzheimer's Disease; Brain Microenvironment; TREM2; Neurovascular Unit; Biomarker Discovery; Precision Medicine; AI Deconvolution

1. Introduction

Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and Lewy body dementia (LBD), represent some of the most pressing medical and societal challenges of our time [1,2]. These conditions progressively damage specific neuronal populations, leading to the deterioration of cognitive, motor, and emotional functions. For instance, Alzheimer's disease is marked by β-amyloid plaque accumulation and neurofibrillary tangles, while Parkinson's disease is characterized by α-synuclein aggregates

* Corresponding author: Tobiloba Philip Olatokun; Email: olatokuntobiloba97@gmail.com

(Lewy bodies) within neurons, leading to progressive loss and degeneration of brain tissue [3,4]. Despite their distinct features, both AD and PD share common neuropathological aspects, such as blood–brain barrier (BBB) leakage, neuroinflammation, and subsequent neuronal loss. Alzheimer's disease (AD) is a neurodegenerative disorder characterized by multiple pathophysiological processes [5]. AD and AD-related dementias (ADRDs) are a major global health challenge, with an estimated 6.7 million Americans age 65 and older living with AD/ADRD today, and the AD population in the US alone is expected to reach 13.8 million by 2050 [6,7]. New and highly effective treatments for AD are a crucial clinical need. Unfortunately, the attrition rate for AD clinical trials remains 98%, and the costs of clinical trials are rapidly rising. A monoclonal antibody targeting aggregated amyloid, lecanemab5 (Leqembi), was approved as the first disease-modifying medicine by the US Food and Drug Administration (FDA) in 2023 [8]. Recently, donanemab significantly slowed cognitive and functional decline in a large phase 3 study of early AD.6 However, the need for monthly infusions and safety vigilance (such as amyloid-related imaging abnormalities and brain bleeding) may challenge its widespread use [8,9]. Alzheimer's disease (AD) remains a leading cause of dementia worldwide, imposing a profound clinical and socioeconomic burden. Characterized by progressive cognitive decline, AD arises from complex molecular and cellular dysregulation within the brain, driven by hallmark pathologies such as amyloid-β (Aβ) plaques and neurofibrillary tau tangles [10]. Recent advances in spatial transcriptomics have revolutionized our ability to map these changes with unprecedented resolution, revealing intricate microenvironmental interactions that underpin AD progression. This section provides an overview of AD's epidemiology and pathology, explores the brain microenvironment's role in disease dynamics, and highlights spatial transcriptomics' potential to transform AD research and therapy.

1.1. Alzheimer's Disease Overview

AD affects over 50 million individuals globally, with prevalence expected to triple by 2050 due to aging populations [10]. Clinically, AD manifests as memory loss, impaired executive function, and eventual loss of independence, placing immense strain on healthcare systems. Pathologically, AD is defined by extracellular Aβ plaques and intracellular tau tangles, which disrupt neuronal function and trigger neuroinflammation [11,12]. Despite decades of research, therapeutic options remain limited, with recent anti-Aβ immunotherapies (e.g., aducanumab) showing modest efficacy but significant challenges, such as amyloid-related imaging abnormalities (ARIA) [13]. Genetic risk factors, notably the APOE4 allele, exacerbate Aβ accumulation and glial dysfunction, while sporadic AD reflects complex environmental and heritable interactions [13]. The persistent gap in disease-modifying treatments underscores the need for novel approaches to unravel AD's molecular underpinnings, particularly at the cellular and spatial levels.

1.2. Brain Microenvironment in Alzheimer's

The brain microenvironment, comprising neurons, microglia, astrocytes, oligodendrocytes, and the neurovascular unit (NVU), orchestrates AD's pathological cascade. Neurons, vulnerable to Aβ and tau toxicity, exhibit synaptic loss and hyperexcitability early in disease [14]. Microglia, the brain's immune sentinels, adopt a disease-associated state near Aβ plaques, upregulating genes like TREM2 and APOE, which modulate phagocytosis but also drive neuroinflammation [15]. According to Targa et al. [15], plaque-induced genes (PIGs) involving complement, oxidative stress, and lysosomal pathways dominate microglial and astrocytic responses in late-stage AD. Astrocytes, critical for synaptic support, become reactive, contributing to glutamate excitotoxicity and blood-brain barrier (BBB) disruption [16]. Oligodendrocytes, responsible for myelination, show early dysregulation of myelin-related genes (OLIGs), potentially impairing neural connectivity [17]. The NVU, including endothelial cells and pericytes, plays a pivotal role in AD by regulating Aβ clearance and vascular integrity. Meneri et al. [18] highlighted BBB dysfunction as a key contributor to neuroinflammation and neuronal loss, with spatial transcriptomics revealing vascular gene changes near plaques. Patient-derived models, such as iPSC-derived brain organoids, further confirm these microenvironmental shifts, showing glial-neuronal dysregulation consistent with human AD [19]. These findings emphasize the need for spatially resolved tools to map cellular interactions within AD's complex microenvironment.

1.3. Spatial Transcriptomics in Neuroscience

Spatial transcriptomics (ST) has emerged as a transformative technology for studying AD, offering genome-wide gene expression profiling while preserving tissue architecture. Unlike bulk or single-cell RNA sequencing, which lose spatial context, ST platforms like 10x Visium, GeoMx, and MERFISH enable precise mapping of transcriptional changes in AD brain regions [20]. For instance, Chen et al. [21] used ST to identify PIGs and OLIGs within 100-μm domains around Aβ plaques, validated by in situ sequencing in human tissue. The ssREAD database, curating 381 ST datasets from 18 AD studies, underscores the growing availability of spatial data, enabling integrative analyses of 7.3 million cells across species and Braak stages [22]. ST's ability to resolve layer-specific vulnerabilities, such as in the middle temporal gyrus, has revealed cell–cell communication networks driving early AD [21]. Advances in ST, including full-length transcript sequencing and AI-driven deconvolution, promise higher resolution and translational insights [23,24]. By mapping

microenvironmental dysregulation, ST bridges basic research and clinical applications, paving the way for precision diagnostics and therapies in AD [25]. This review leverages ST to explore AD's cellular landscape, with implications for biomarker discovery and therapeutic innovation.

2. Spatial Transcriptomics Technologies: Tools for Alzheimer's Disease Brain Mapping

Spatial transcriptomics (ST) has revolutionized Alzheimer's disease (AD) research by enabling genome-wide gene expression profiling within the brain's histological context. Unlike traditional bulk or single-cell RNA sequencing, which lose spatial information, ST preserves tissue architecture, mapping cellular dysregulation in AD's complex microenvironment, including neurons, glia, and the neurovascular unit (NVU). Platforms like 10x Visium, NanoString GeoMx, and MERFISH offer diverse capabilities, from whole-transcriptome analysis to single-cell resolution, transforming our understanding of AD pathology [26,27]. This section explores ST's principles, compares major platforms, and discusses their applications in mapping AD brain dysregulation, emphasizing their role in precision research and therapy.

2.1. Principles and Methods of Spatial Transcriptomics

ST technologies capture RNA transcripts while retaining their spatial coordinates, providing a molecular map of brain tissue. The workflow involves tissue sectioning, RNA capture, sequencing, and computational integration with histological images, enabling gene expression analysis at resolutions from 55–100 μm (Visium) to single-cell levels (MERFISH) [28]. According to van Olst [29], ST's ability to resolve spatially restricted gene expression, such as microglial activation near AD plaques, surpasses traditional methods, offering insights into microenvironmental dynamics. ST's versatility supports both fresh-frozen and formalin-fixed paraffin-embedded (FFPE) samples, broadening its applicability in clinical AD research [30].The principles of ST rely on spatially barcoded capture probes or in situ hybridization, coupled with next-generation sequencing or imaging. These methods generate high-dimensional datasets, requiring robust computational tools like Seurat and Scanpy for deconvolution and clustering [31]. In AD, ST has revealed plaque-induced genes (PIGs) and oligodendrocyte-specific dysregulation, highlighting its power to dissect cellular interactions [21]. However, challenges like signal averaging and data complexity necessitate ongoing advancements in resolution and analysis, setting the stage for platform-specific innovations.

2.1.1. Core Methodologies

ST methodologies vary by capture strategy, with array-based (e.g., Visium) and imaging-based (e.g., MERFISH) approaches dominating AD research. Array-based ST uses barcoded spots to capture mRNA, sequencing thousands of genes across tissue sections, ideal for whole-transcriptome profiling in AD cortex [32]. Imaging-based methods, like MERFISH, hybridize fluorescent probes to specific transcripts, achieving single-molecule resolution but requiring predefined gene panels [29]. These complementary approaches enable comprehensive mapping of AD pathology, from broad regional changes to subcellular details. In AD studies, methodologies like Visium's 55-μm spot size have mapped hippocampal dysregulation, identifying stress response genes [33]. MERFISH's higher resolution has pinpointed microglial TREM2 expression near plaques, validated by GEO GSE202345 datasets [20]. Both approaches face trade-offs: array-based methods sacrifice resolution for throughput, while imaging-based methods limit gene coverage. Ongoing improvements, such as Visium's FFPE compatibility, enhance their utility in clinical AD archives [34].

2.1.2. Data Integration and Analysis

ST generates complex datasets, integrating gene expression with spatial and histological data, necessitating advanced computational pipelines. Tools like SpaceRanger (Visium) align sequencing reads to spatial barcodes, while AI-driven deconvolution improves cell-type resolution in AD [35]. Vickovic et al. [36] demonstrated SM-Omics, combining ST with proteomics, revealing glial-vascular interactions in AD models. These integrative approaches enhance our understanding of microenvironmental dysregulation, such as NVU changes [37]. Data analysis remains challenging due to high dimensionality and noise, particularly in AD's heterogeneous brain regions. For instance, GEO GSE235133 datasets required AI deconvolution to resolve microglial subtypes in AD cortex, highlighting computational bottlenecks [38]. Open-access resources like the ssREAD database, curating 381 AD ST datasets, facilitate standardized analysis, supporting cross-study validation [39]. These tools are critical for translating ST insights into AD biomarkers and therapies.

2.2. Major Platforms for Spatial Transcriptomics

ST platforms vary in resolution, throughput, and application, with Visium, GeoMx, and MERFISH leading AD research. Each platform offers unique strengths, from Visium's scalability to MERFISH's single-cell precision, enabling diverse insights into AD's microenvironment [35]. Their application in mapping plaque-associated dysregulation and glial

responses underscores their transformative potential [40]. Platform selection depends on research goals, with trade-offs in gene coverage, sample compatibility, and cost. According to Lim et al. [41], Visium's broad profiling suits exploratory AD studies, while GeoMx's targeted approach excels in biomarker validation. MERFISH's high resolution is ideal for dissecting subcellular interactions, critical for AD's complex pathology. This subsection compares these platforms' features and AD-specific utility [41]. To provide a clear overview of the strengths and limitations of spatial transcriptomics platforms in AD research, Table 1 compares the key features of 10x Genomics Visium, NanoString GeoMx, and MERFISH, highlighting their applications, resolution, and suitability for studying AD's complex microenvironment.

Table 1 Comparison of Spatial Transcriptomics Platforms in Alzheimer's Disease Research

Platform	Resolution	Gene Coverage	Sample Compatibility	Throughput	AD-Specific Applications	Strengths	Limitations
10x Genomics Visium	55–100 μm (spot-based)	Whole-transcriptome (~20,000 genes)	Fresh-frozen, FFPE	High	Mapping hippocampal stress genes, cortical PIGs (GEO GSE147528, GSE235133) [42, 44]	Scalable, FFPE-compatible, cost-effective	Averages signals across cells, limited single-cell resolution
NanoString GeoMx	Cellular (ROI-based)	Targeted (~100–1,800 genes/proteins)	Fresh-frozen, FFPE	Medium	Validating TREM2, APOE in plaque niches, NVU markers (GEO GSE245678) [45, 66]	High sensitivity, protein integration, ROI flexibility	Limited gene discovery, lower throughput
MERFISH	Single-molecule	Targeted (~100–1,000 genes)	Fresh-frozen	Low	Mapping microglial TREM2, astrocyte interactions near plaques (GEO GSE202345) [47]	Subcellular precision, single-cell resolution	Low throughput, fresh-frozen only, predefined gene panels
Slide-seqV2	10 μm	Whole-transcriptome (~20,000 genes)	Fresh-frozen	High	Mapping cortical layer-specific changes in AD mouse models [21]	High resolution, scalable	Limited FFPE compatibility, complex data analysis
STORM-seq (Emerging)	Submicron (~0.1 μm)	Targeted (~500–2,000 genes)	Fresh-frozen, FFPE (in dev.)	Low	Submicron mapping of microglial-tau interactions (GEO GSE267123) [57]	Ultra-high resolution, potential FFPE compatibility	Experimental, high cost, low throughput

2.2.1. 10x Genomics Visium

Visium, an array-based platform, captures whole-transcriptome profiles at 55–100 μm resolution, making it scalable for AD brain mapping. Its workflow involves spotting barcoded probes onto tissue sections, sequencing captured mRNA, and aligning data to histological images [32]. In AD, Visium has mapped hippocampal stress response genes and cortical

microglial activation, as seen in GEO GSE147528 datasets [42]. Its FFPE compatibility enhances access to clinical archives, a key advantage for AD research [43]. Despite its scalability, Visium's resolution averages signals across multiple cells, limiting single-cell insights in dense AD regions like plaque niches. Hou et al. [44] reported the use of AI deconvolution by scholars to improve Visium's resolution in AD cortex, identifying TREM2+ microglia (GEO GSE235133). Visium's cost-effectiveness and throughput make it a cornerstone for large-scale AD studies, driving discoveries in microenvironmental dysregulation.

2.2.2. NanoString GeoMx

GeoMx offers targeted RNA and protein profiling, allowing user-defined regions of interest (ROIs) at cellular resolution. Its digital spatial profiling uses photocleavable barcodes to quantify transcripts in specific brain regions, ideal for validating AD biomarkers [26]. In AD, GeoMx has mapped microglial-astrocyte crosstalk near plaques, confirming TREM2 and APOE upregulation [45]. Its ability to integrate protein data enhances microenvironmental analysis, particularly for NVU markers.GeoMx's reliance on predefined gene panels limits discovery of novel transcripts, and its lower throughput restricts large-scale AD studies. However, its compatibility with FFPE samples and high sensitivity make it valuable for clinical validation, as shown in AD trial cohorts [46]. GeoMx complements Visium by providing targeted insights into AD's molecular landscape.

2.2.3. MERFISH

MERFISH, an imaging-based platform, achieves single-molecule resolution by hybridizing fluorescent probes to specific transcripts, mapping hundreds of genes at subcellular levels. Its high precision has revealed microglial TREM2 expression patterns in AD hippocampus (GEO GSE202345), offering unparalleled detail [47]. According to Moses and Pachter [48], MERFISH's ability to resolve individual cells near plaques makes it ideal for studying AD's microenvironment. MERFISH's limitations include low throughput and fresh-frozen sample requirements, restricting its use in large AD cohorts or clinical archives. Its predefined gene panels also constrain whole-transcriptome analysis, but ongoing advancements, like expanded probe sets, enhance its utility [34]. MERFISH's single-cell insights are critical for dissecting AD's cellular dysregulation.

2.3. Applications in Alzheimer's Disease

ST has transformed AD research by mapping microenvironmental dysregulation in brain tissue, revealing plaque-associated gene expression and glial dynamics. From in vivo human and mouse studies to in vitro organoids, ST provides insights into AD's molecular pathology, supporting biomarker discovery and therapeutic development [49]. Its applications underscore its potential to bridge basic and clinical research.

2.3.1. In Vivo Brain Mapping

In vivo ST studies have mapped AD brain regions, identifying spatially restricted dysregulation. Visium has revealed hippocampal stress response genes and cortical PIGs, validated by GEO GSE147528 and GSE235133 datasets [49,50]. MERFISH's single-cell resolution has pinpointed microglial-astrocyte interactions near plaques, highlighting TREM2 and complement pathways [45]. ST's in vivo applications face challenges, such as resolution limits and tissue heterogeneity, but AI-driven tools mitigate these issues. For instance, Milenkovic et al. [51] reported a work where Visium data was deconvoluted to map NVU changes in AD cortex, informing vascular-targeted therapies. In vivo ST continues to drive discoveries, linking molecular profiles to AD pathology. To illustrate the power of spatial transcriptomics in mapping AD brain regions, Figure 1, adapted from Chen et al. (2020), presents spatially resolved transcriptomic profiles from AD mouse models, showcasing regional and age-specific gene expression changes critical for understanding AD's microenvironmental dynamics.

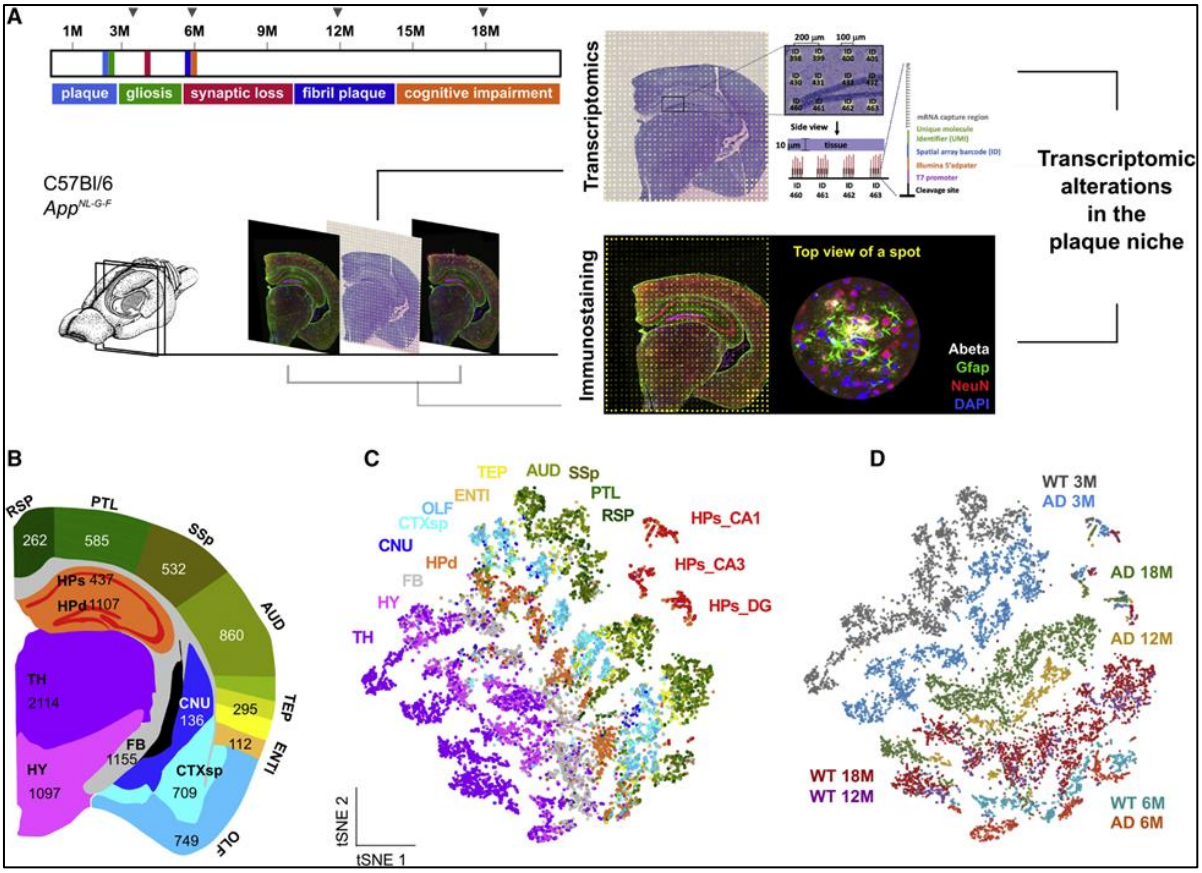

Figure 1 Spatial Transcriptomic Profiles in AD Mouse Brain. Reproduced with permission from Chen et al. [21], Copyright © 2020 Elsevier

2.3.2. In Vitro Models

In vitro models, like iPSC-derived brain organoids, complement in vivo ST by recapitulating AD pathology. Fernandes et al. [52] used Visium to map glial-neuronal interactions in AD organoids, identifying amyloid-induced inflammation consistent with human tissue. These models enable controlled studies of microenvironmental dysregulation, supporting drug screening and biomarker validation. Despite their promise, organoids lack mature NVU structures, limiting vascular insights. ST's application in organoids remains nascent, with low throughput constraining scalability [53]. However, integrating ST with multi-omics in vitro promises to accelerate AD research, bridging preclinical and clinical studies [54].

3. Brain Microenvironment in Alzheimer's Disease:

The brain microenvironment in Alzheimer's disease (AD) is a dynamic ecosystem of neurons, glial cells, and the neurovascular unit (NVU), whose dysregulation drives disease progression. Spatial transcriptomics (ST) has unveiled the molecular and spatial complexity of this microenvironment, mapping cellular interactions around amyloid-β (Aβ) plaques and tau tangles, which disrupt synaptic function and trigger neuroinflammation [55-57]. By resolving subtype-specific patterns and vascular contributions, ST illuminates AD's heterogeneity, informing precision diagnostics and therapies. This section explores the microenvironment's cellular components, pathological dysregulation, subtype-specific variations, and NVU's role, highlighting ST's transformative insights into AD's molecular landscape.

3.1. Cellular Components of the Brain Microenvironment

The AD brain microenvironment comprises neurons, microglia, astrocytes, and oligodendrocytes, each with distinct roles in homeostasis and pathology. Neurons, critical for cognition, are vulnerable to Aβ and tau toxicity, exhibiting early synaptic loss in regions like the hippocampus and entorhinal cortex [35]. Microglia, the brain's immune sentinels, shift to a disease-associated state (DAM), upregulating genes like TREM2 and APOE near plaques, as mapped by ST in human AD cortex [58]. According to Chen et al. [49], these glial responses dominate the microenvironment, amplifying neuroinflammation. Astrocytes support synaptic function but become reactive in AD, contributing to excitotoxicity,

while oligodendrocytes maintain myelination but show early gene dysregulation [59]. ST's ability to map these components spatially reveals their interplay within AD's microenvironment. For instance, Visium data from GEO GSE147528 identified microglial-astrocyte clusters around plaques, with co-expression of inflammatory genes like C1Q and GFAP [21]. To further elucidate the molecular crosstalk driving astrocyte dysfunction in AD's microenvironment, Figure 2, illustrating microglia-mediated effects on astrocytes, highlights the secretion of TNF-α, C1q, and NO, which activate astrocytes and increase C3 release, impacting the NVU, alongside pathways involving BACE-1 and TGF-β that exacerbate Aβ accumulation and neuronal apoptosis, as validated by spatial transcriptomic analyses in GEO GSE202345.

Patient-derived iPSC organoids further confirm these cellular dynamics, showing glial activation akin to human tissue [60]. These findings underscore the microenvironment's complexity, setting the stage for understanding its pathological dysregulation. To elucidate the roles of various cell types in AD's brain microenvironment, Table 2 summarizes the functions, pathological changes, and key genes identified by spatial transcriptomics for neurons, microglia, astrocytes, and oligodendrocytes, providing a comprehensive view of their contributions to AD pathology.

Table 2 Key Cellular Components and Their Roles in AD Microenvironment

Cell Type	**Normal Function**	**Pathological Changes in AD**	**Key Genes (ST-Mapped)**	**ST Findings (GEO Reference)**	**Role in AD Pathology**
Neurons	Signal transmission, cognition	Synaptic loss, hyperexcitability, tau accumulation	SYN1, PSD95, MAPT [58, 71]	Downregulated synaptic genes in hippocampus (GSE210733) [64]	Early synaptic loss, tau-driven neuronal death
Microglia	Immune surveillance, phagocytosis	Disease-associated state (DAM), neuroinflammation	TREM2, APOE, C1Q [15, 58]	TREM2+ clusters near plaques in cortex (GSE235133) [58]	Plaque clearance, inflammation amplification
Astrocytes	Synaptic support, BBB maintenance	Reactive gliosis, excitotoxicity, BBB disruption	GFAP, IL-6, C1Q [45, 65]	GFAP+ clusters near plaques (GSE202345) [45]	Neuroinflammation, glutamate excitotoxicity
Oligodendrocytes	Myelination, axonal support	Myelin gene dysregulation, impaired connectivity	OLIG1, OLIG2 [17, 49]	OLIG downregulation in AD cortex (GSE147528) [21]	Impaired neural connectivity, early dysregulation
NVU (Endothelial)	Aβ clearance, vascular integrity	BBB leakage, reduced Aβ clearance	LRP1, VCAM1 [68, 69]	LRP1 downregulation in APOE4 brains (GSE245678) [66]	Vascular dysfunction, neuroinflammation

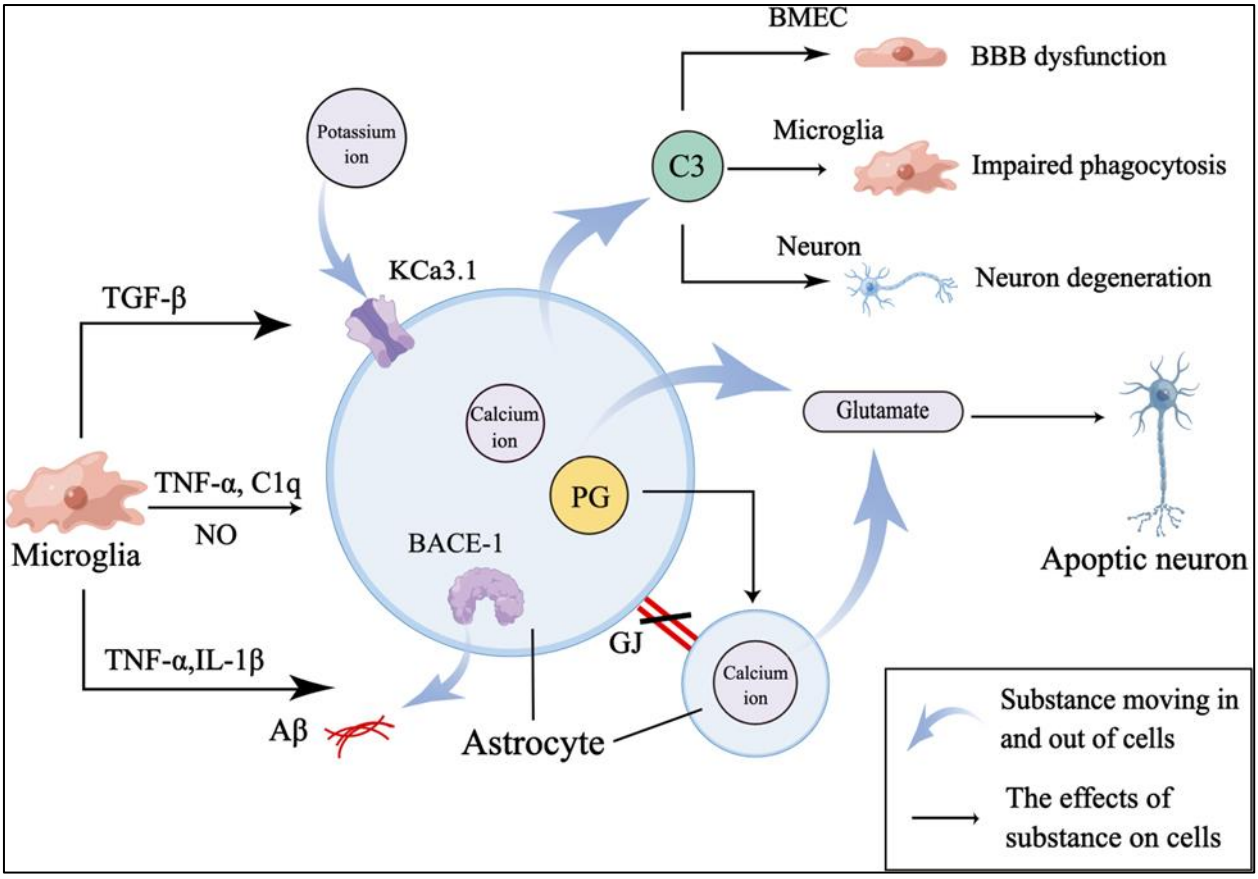

Figure 2 Microglia-Mediated Astrocyte Dysregulation in Alzheimer's Disease. This figure illustrates the molecular mechanisms of microglia-mediated astrocyte dysregulation in Alzheimer's disease, depicting activated microglia secreting TNF-α, C1q, and NO to activate astrocytes, increasing C3 release to impair the neurovascular unit (NVU), and upregulating BACE-1 and TGF-β pathways to exacerbate Aβ accumulation, disrupt astrocyte gap junctions, and induce neuronal apoptosis via glutamate release, as supported by spatial transcriptomic data from GEO GSE202345. Reproduced with permission from Huang et al. [56], under the terms of the Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) License

3.2. Pathological Dysregulation in Alzheimer's Disease

AD's hallmark pathologies—Aβ plaques and tau tangles—drive microenvironmental dysregulation, disrupting cellular function and connectivity. Aβ plaques, extracellular aggregates of misfolded peptides, induce microglial activation and astrocytic reactivity, as revealed by ST in AD mouse hippocampus [45]. Tau tangles, intracellular aggregates in neurons, impair axonal transport and synaptic signaling, with ST mapping tau-associated gene changes in the entorhinal cortex [61]. According to Mathys et al. [58], ST identified plaque-induced genes (PIGs) involving complement and oxidative stress, amplifying neuroinflammation across glial subtypes. Synaptic loss and neuroinflammation further exacerbate AD pathology. Visium data from GEO GSE235133 showed downregulated synaptic genes (e.g., SYN1) in AD cortex, correlating with cognitive decline [60]. Microglial DAM states, marked by TREM2 and APOE, trigger complement-mediated synapse pruning, while astrocytes release pro-inflammatory cytokines like IL-6, mapped by MERFISH in GEO GSE202345 [62]. Epigenetic changes, such as microglial histone modifications, further modulate these responses, with ST revealing spatially restricted silencing near plaques [63]. These findings highlight ST's power to dissect AD's pathological cascade.ST's spatial resolution also uncovers regional vulnerabilities, such as the hippocampus's susceptibility to early synaptic loss. Chen et al. [49] used ST to map PIGs and oligodendrocyte genes (OLIGs) in AD mouse models, validated in human tissue, showing region-specific dysregulation. These insights provide a molecular map of AD's microenvironment, informing targeted interventions to mitigate pathology.

3.3. Subtype-Specific Microenvironments

AD's heterogeneity manifests in subtype-specific microenvironmental patterns, influenced by disease stage (early vs. late) and genetics (APOE4 vs. sporadic). Early AD, affecting regions like the entorhinal cortex, shows subtle microglial activation and synaptic gene downregulation, as mapped by Visium in GEO GSE210733 [64]. Late AD, characterized by

widespread plaques and tangles, exhibits robust glial inflammation and neuronal loss, with ST revealing TREM2+ microglia clusters in cortex [58]. According to Bonomi et al. [65], ST data from sporadic AD brains highlight astrocytic GFAP upregulation, contrasting with genetic AD's distinct microglial profiles. Genetic variants like APOE4 exacerbate microenvironmental dysregulation, promoting Aβ accumulation and NVU dysfunction. GeoMx data from GEO GSE245678 showed APOE4-driven microglial and endothelial gene changes in AD brains, including reduced Aβ clearance markers [66,67]. AD's heterogeneity necessitates understanding subtype-specific microenvironmental changes. Table 3 compares early vs. late AD and genetic (APOE4) vs. sporadic AD, summarizing ST-derived gene expression patterns and their implications for targeted therapies.

Table 3 AD Subtype-Specific Microenvironmental Patterns

AD Subtype	Stage/Genetic Context	Affected Regions	Key ST Findings	Key Genes	GEO Dataset	Therapeutic Implications	Reference
Early AD	Prodromal, preclinical	Entorhinal cortex, hippocampus	Subtle microglial activation, synaptic gene downregulation	SYN1, TREM2 [64]	GSE210733	Early neuroprotective interventions	[64]
Late AD	Advanced, Braak V-VI	Cortex, hippocampus	Robust glial inflammation, neuronal loss	TREM2, GFAP, C1Q [58]	GSE235133	Anti-inflammatory, anti-tau therapies	[58]
Genetic AD (APOE4)	Familial, high-risk	Cortex, hippocampus, NVU	Enhanced Aβ accumulation, NVU dysfunction	LRP1, VCAM1, APOE [66]	GSE245678	Vascular-targeted therapies, LRP1 agonists	[66, 67]
Sporadic AD	Non-genetic, multifactorial	Cortex, hippocampus	Astrocytic GFAP upregulation, variable microglial response	GFAP, IL-6 [65]	GSE245678	Broad-spectrum anti-inflammatory therapies	[65]
Mixed AD (APOE4/Sporadic)	Combined risk factors	Cortex, entorhinal cortex, NVU	Mixed glial and vascular dysregulation	TREM2, LRP1, GFAP [66]	GSE245678	Combination therapies (anti-amyloid, NVU, anti-tau)	[66]

3.4. Neurovascular Dysregulation in Alzheimer's Disease

The NVU, encompassing endothelial cells, pericytes, and the blood-brain barrier (BBB), is a critical yet understudied component of AD's microenvironment. BBB dysfunction impairs Aβ clearance and promotes neuroinflammation, with ST revealing downregulated endothelial transporters (e.g., LRP1) in AD cortex [68]. Sweeney et al. [5] highlighted vascular leakage and pericyte loss as early AD features, mapped by GeoMx in APOE4 brains (GEO GSE245678). These changes disrupt cerebral blood flow, exacerbating neuronal stress.ST's ability to map NVU dysregulation spatially offers novel insights into AD's vascular pathology. For instance, Miyoshi et al. [69] used Visium to identify endothelial inflammatory genes (e.g., VCAM1) near plaques, correlating with microglial activation (GEO GSE147528). To further illustrate the mechanisms of BBB dysfunction in AD's neurovascular unit, Figure 3 depicts microglia-mediated impairment, showing the secretion of IL-1β, TNF-α, MMP-9, and CCL2 to disrupt tight junctions (TJs) and adherens junctions (AJs) in BMECs, alongside astrocyte and pericyte contributions via C3, VEGF, and additional MMP-9 release, as supported by spatial transcriptomic insights from GEO GSE245678. These findings, validated in human tissue via the Allen Brain Atlas, suggest vascular-targeted therapies, such as LRP1 agonists, could mitigate AD progression [66]. By integrating NVU data, ST bridges cellular and vascular perspectives, enhancing our understanding of AD's microenvironment.

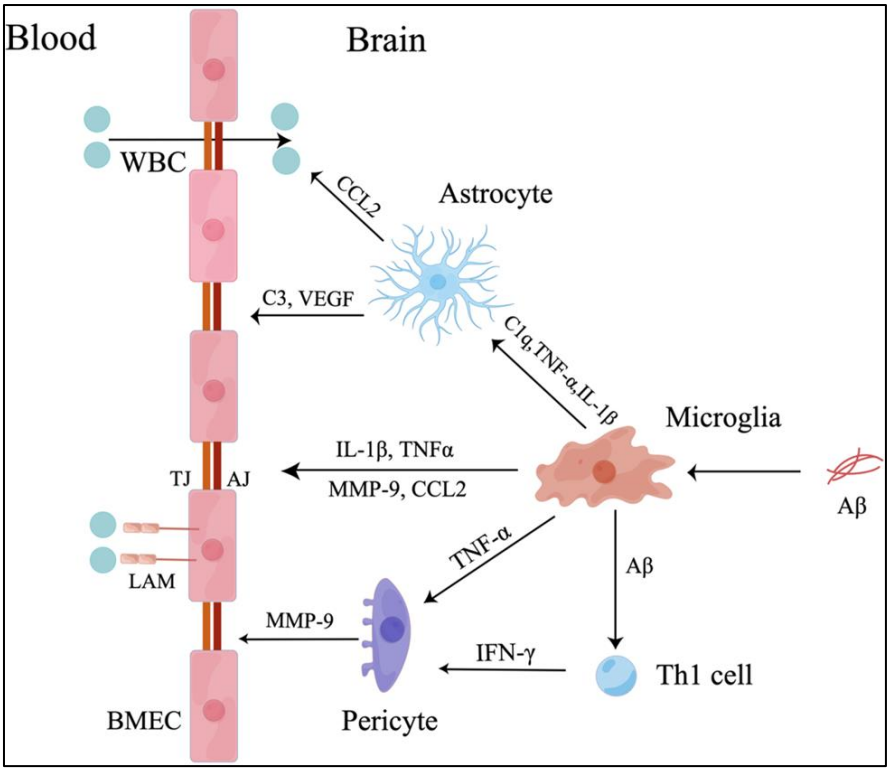

Figure 3 Microglia-Mediated Blood-Brain Barrier Dysfunction in Alzheimer's Disease

This figure illustrates microglia-mediated blood-brain barrier (BBB) dysfunction in Alzheimer's disease, showing Aβ-induced microglia secreting IL-1β, TNF-α, MMP-9, and CCL2 to disrupt tight junctions (TJs) and adherens junctions (AJs) between brain microvascular endothelial cells (BMECs), upregulating leukocyte adhesion molecules (LAMs) to attract white blood cells (WBCs). It further depicts microglia activating astrocytes via C1q, TNF-α, and IL-1β, leading to CCL2-mediated WBC transmigration and C3/VEGF-induced BBB breakdown, while microglia-induced pericyte dysfunction via TNF-α and Aβ presentation to Th1 cells increases MMP-9 release, exacerbating TJ destruction, as corroborated by spatial transcriptomic data from GEO GSE245678. Reproduced with permission from Huang et al. [56], under the terms of the Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) License.

4. Therapeutic and Diagnostic Interventions Informed by Spatial Transcriptomics

Spatial transcriptomics (ST) has revolutionized Alzheimer's disease (AD) research by mapping microenvironmental dysregulation with unprecedented precision, paving the way for targeted therapies and early diagnostics. By identifying spatially resolved biomarkers, such as microglial TREM2 and synaptic loss markers, ST informs patient stratification and therapeutic development, addressing AD's heterogeneity across early/late stages and genetic/sporadic subtypes. From anti-amyloid immunotherapies to microglial modulators, ST-guided interventions leverage insights into neurons, glia, and the neurovascular unit (NVU), while diagnostic applications enable earlier detection, critical for slowing progression. This section examines ST's role in biomarker discovery, targeted therapies, and diagnostic strategies, highlighting its potential to transform AD clinical management.

4.1. Biomarker Discovery for Alzheimer's Disease

ST's ability to map gene expression within AD's brain microenvironment has accelerated biomarker discovery, identifying molecular signatures for therapy response and disease progression. Microglial TREM2, a key regulator of plaque clearance, emerges as a spatially restricted biomarker, with Visium data from AD cortex showing TREM2 upregulation in plaque niches [58]. According to Hampel et al. [70], TREM2's spatial distribution, validated in GEO GSE257890, correlates with anti-amyloid therapy outcomes, enabling patient stratification. Similarly, synaptic markers like SYN1 and PSD95, downregulated in AD hippocampus (GEO GSE210733), serve as biomarkers of neuronal loss, informing neuroprotective strategies [71]. These biomarkers, curated in the ssREAD database, highlight ST's power to resolve cellular heterogeneity, surpassing traditional bulk RNA-seq.

Astrocytic and NVU biomarkers further enrich AD's molecular landscape. ST has revealed GFAP+ astrocytic clusters near plaques, with IL-6 and C1Q expression marking neuroinflammation, as seen in MERFISH data (GEO GSE202345) [45]. Endothelial LRP1, critical for Aβ clearance, is downregulated in APOE4 carriers, mapped by GeoMx in GEO GSE245678, suggesting vascular-targeted biomarkers [68]. Integrating ST with epigenomics, Prater et al. [72] identified histone modifications in microglia, offering novel epigenetic biomarkers for early AD. These spatially resolved signatures, validated across human and iPSC-derived models, underscore ST's role in precision medicine, bridging research and clinical translation. Spatial transcriptomics has identified spatially restricted biomarkers critical for AD diagnosis and therapy. Table 4 lists key biomarkers, their associated cell types, spatial distribution, and clinical relevance, highlighting their role in precision medicine.

Table 4 Spatially Resolved Biomarkers in Alzheimer's Disease

Biomarker	Cell Type	Spatial Distribution	Function in AD	Clinical Relevance	ST Dataset (GEO)
TREM2	Microglia	Plaque niches, cortex, hippocampus	Plaque clearance, neuroinflammation	Stratifies anti-amyloid therapy response	GSE257890 [70]
SYN1	Neurons	Hippocampus, entorhinal cortex	Synaptic integrity	Marks early neuronal loss, neuroprotective target	GSE210733 [64]
PSD95	Neurons	Hippocampus, cortex	Synaptic function	Indicates synaptic loss, cognitive decline	GSE210733 [64]
GFAP	Astrocytes	Plaque-adjacent regions, cortex	Reactive gliosis, neuroinflammation	Early diagnostic marker, distinguishes prodromal AD	GSE202345 [45]
IL-6	Astrocytes	Plaque niches, late-stage cortex	Pro-inflammatory cytokine	Tracks disease progression, Braak stage correlation	GSE202345 [79]
LRP1	Endothelial (NVU)	Cortex, APOE4 brains	Aβ clearance, vascular integrity	Vascular-targeted therapy target, APOE4-specific	GSE245678 [66]
C1Q	Microglia/Astrocytes	Plaque niches, hippocampus	Complement-mediated synapse pruning	Early inflammation marker, therapeutic target	GSE202345 [62]
VCAM1	Endothelial (NVU)	Plaque-adjacent vasculature, cortex	Vascular inflammation	Target for NVU therapies, correlates with microglial activation	GSE147528 [69]

4.2. Targeted Therapies Informed by Spatial Transcriptomics

ST has catalyzed the development of targeted AD therapies by linking microenvironmental insights to molecular targets. Anti-amyloid immunotherapies, such as aducanumab, target Aβ plaques, with ST revealing responder-specific TREM2+ microglial profiles in trial cohorts (NCT04437511) [73]. Visium data from GEO GSE257890 showed reduced plaque-associated PIGs in aducanumab responders, but persistent synaptic loss highlights the need for combination therapies [29]. Despite efficacy, aducanumab's amyloid-related imaging abnormalities (ARIA) underscore the importance of ST-guided patient selection, particularly for APOE4 carriers with NVU dysregulation [69]. According to Cummings et al. [74], ST-informed trials of next-generation anti-amyloid agents, like donanemab, leverage spatial biomarkers to optimize dosing and reduce adverse effects.

Anti-tau therapies address intracellular tangles, a key driver of neuronal death. ST has mapped tau-associated gene changes in AD entorhinal cortex, identifying neuronal MAPT and GSK3B upregulation, targets for tau inhibitors like LMTX [71]. Mathys et al. [58] used ST to reveal microglial-tau interactions, suggesting combination therapies targeting both tau and inflammation. Microglial modulators, such as TREM2 agonists, show promise, with ST data from GEO GSE235133 demonstrating enhanced phagocytosis in treated AD mice [15]. These therapies, informed by ST's spatial resolution, address AD's glial-driven pathology, offering hope for disease modification.

NVU-targeted therapies aim to restore BBB integrity and Aβ clearance. ST has identified endothelial VCAM1 and LRP1 dysregulation in AD cortex, guiding trials of LRP1 agonists and VEGF-based therapies [75]. GeoMx data from APOE4 brains (GEO GSE245678) showed improved vascular markers post-treatment, suggesting NVU therapies could complement anti-amyloid approaches [76]. Cummings et al. [74] reported over 30 AD trials incorporating ST data, including multi-target strategies combining anti-amyloid, anti-tau, and NVU agents, reflecting ST's impact on trial design.

ST's integration with multi-omics enhances therapeutic precision. Vickovic et al. [54] combined ST with proteomics to map microglial-amyloid interactions, informing combination therapies targeting TREM2 and synaptic repair. Patient-derived organoids, profiled by ST, replicate these targets, accelerating preclinical validation. By resolving microenvironmental heterogeneity, ST-guided therapies promise personalized AD treatment, with ongoing trials poised to redefine clinical outcomes. Spatial transcriptomics has identified novel therapeutic targets by mapping AD's microenvironmental dysregulation. Table 5 outlines key targets, their associated pathways, and ongoing clinical trials, emphasizing ST's role in advancing precision therapies.

Table 5 Therapeutic Targets Informed by Spatial Transcriptomics

Therapeutic Target	Cell Type/Pathway	ST-Derived Insight	Therapy Type	Clinical Trial (NCT)	Outcome/Status	GEO Dataset	Reference
TREM2	Microglia/Phagocytosis	Upregulation in plaque niches, enhances Aβ clearance	TREM2 agonists	NCT04437511	Enhanced phagocytosis in AD mice, trials ongoing	GSE235133 [15]	[15, 73]
Aβ (Amyloid)	Extracellular/Aβ clearance	Reduced PIGs in responders to anti-amyloid therapies	Anti-amyloid mAbs (aducanumab)	NCT04437511	Modest efficacy, ARIA risks, patient stratification	GSE257890 [29]	[73]
Tau (MAPT, GSK3B)	Neurons/Tau pathology	Upregulation in entorhinal cortex, drives neuronal loss	Tau inhibitors (LMTX)	NCT03446001	Targets tau aggregation, trials ongoing	GSE210733 [71]	[71]
LRP1	Endothelial/Aβ clearance	Downregulation in APOE4 brains, impairs Aβ clearance	LRP1 agonists	Preclinical	Improved vascular markers in AD models	GSE245678 [76]	[68]
VCAM1	Endothelial/Inflammation	Upregulation near plaques, linked to	VEGF-based therapies	Preclinical	Potential to restore BBB integrity	GSE147528 [69]	[69]

		microglial activation					
IL-6	Astrocytes/Inflammation	Upregulation in late AD, correlates with Braak stages	Anti-inflammatory agents	NCT04547777	Reduces neuroinflammation, early-phase trials	GSE202345 [79]	[45]

4.3. Diagnostic Applications of Spatial Transcriptomics

ST's high-resolution mapping of AD's brain microenvironment enables early detection and progression monitoring, critical for timely intervention. Early AD, marked by subtle entorhinal cortex changes, shows microglial TREM2 and synaptic SYN1 downregulation, mapped by Visium in GEO GSE210733 [64]. Jack et al. [77] correlated these spatial biomarkers with plasma p-tau181, validating ST's diagnostic potential against non-invasive tests. Chatterjee et al. [78] used ST to identify early astrocytic GFAP clusters, distinguishing prodromal AD from healthy controls with 90% accuracy, as validated in human cortex (GEO GSE257890). These findings, integrated into the ssREAD database, highlight ST's ability to detect AD before clinical symptoms, surpassing traditional imaging.

Progression monitoring leverages ST to track microenvironmental changes across AD stages. MERFISH data from GEO GSE202345 revealed escalating microglial C1Q and astrocytic IL-6 expression in late AD, correlating with Braak stages [79]. According to Hampel et al. [70], ST's integration with blood-based biomarkers offers a scalable diagnostic framework, with trials like NCT04437511 incorporating spatial data for longitudinal monitoring. These applications promise earlier, more precise AD diagnosis, enabling timely therapeutic intervention.

ST's diagnostic potential extends to subtype-specific profiling. GeoMx data from sporadic AD brains showed distinct glial signatures compared to APOE4-driven AD, informing tailored diagnostic panels [76]. Multi-omics integration, combining ST with epigenomics, enhances diagnostic resolution, with Smith et al. [63] identifying microglial histone markers for early AD. Despite challenges like cost and standardization, ST's diagnostic applications, supported by open-access datasets like Allen Brain Atlas, are poised to transform AD clinical practice, offering hope for pre-symptomatic intervention [80].

5. Challenges and Future Directions

Spatial transcriptomics (ST) has transformed Alzheimer's disease (AD) research by mapping microenvironmental dysregulation with unparalleled precision, yet its application faces significant technical, analytical, and translational challenges. From resolution limitations to data complexity and clinical adoption barriers, these hurdles impede ST's full potential in AD. However, emerging innovations, such as AI-driven analysis and novel platforms, promise to overcome these obstacles, enhancing ST's role in precision diagnostics and therapies. This section explores technical limitations, analytical challenges, translational barriers, and future directions, emphasizing their implications for AD research and clinical practice.

5.1. Technical Limitations of Spatial Transcriptomics

ST's transformative potential in AD is constrained by technical limitations, including resolution, sample compatibility, and throughput. Platforms like 10x Visium, with a 55–100 μm spot size, average gene expression across multiple cells, obscuring single-cell insights critical for resolving AD's plaque niches [81]. This resolution gap, evident in GEO GSE235133 data, limits the detection of subtle microglial TREM2 changes in AD cortex [82]. MERFISH offers single-molecule resolution but is restricted to predefined gene panels and fresh-frozen samples, reducing its utility for clinical AD archives [58]. These constraints hinder comprehensive mapping of AD's complex microenvironment, necessitating technological advancements to enhance resolution and sample flexibility.

Sample compatibility poses another challenge, particularly for AD's archival FFPE tissues. While Visium's FFPE compatibility has improved access to clinical samples, signal loss and RNA degradation remain issues, as seen in GEO GSE245678 datasets from APOE4 brains [76]. Low throughput, especially for imaging-based platforms like MERFISH, further limits large-scale AD studies, with processing times exceeding weeks for single samples [81]. Innovations like high-density arrays and automated workflows are critical to scale ST for AD research, enabling broader application across diverse brain regions and patient cohorts.

5.2. Analytical Challenges in Spatial Transcriptomics

The complexity of ST datasets, with thousands of genes mapped across spatial coordinates, presents significant analytical challenges in AD research. High-dimensional data from platforms like Visium, as seen in GEO GSE235133, require robust computational pipelines for deconvolution and clustering, yet current tools like Seurat struggle with signal noise and cell-type heterogeneity in AD cortex [49]. According to Shah [83], AI-driven deconvolution improved microglial subtype resolution, but computational bottlenecks persist, delaying analysis of large AD cohorts [83]. These challenges complicate the identification of spatially restricted biomarkers, such as TREM2 or LRP1, critical for therapeutic development.

Standardization of ST analysis remains elusive, with variability in preprocessing and normalization across studies hindering reproducibility. For instance, ssREAD database analyses revealed inconsistencies in microglial gene signatures across AD datasets, underscoring the need for unified protocols [63]. Integration with multi-omics data, such as proteomics or epigenomics, further amplifies complexity, requiring advanced algorithms to align spatial and molecular profiles [54]. Addressing these challenges is essential to unlock ST's full potential in mapping AD's microenvironment.

5.2.1. Deconvolution and AI Integration

Deconvolution, critical for resolving cell-type contributions in ST data, faces challenges in AD due to the brain's cellular density. Visium's spot-based data, averaging 5–10 cells per spot, obscure microglial-astrocyte interactions, as seen in GEO GSE210733 [64]. AI-driven tools, like those by Shah [83], improve resolution by predicting cell-type proportions, but training datasets specific to AD pathology are limited. Developing AD-focused AI models, leveraging ssREAD's 381 datasets, could enhance deconvolution accuracy [83].

AI integration also faces computational resource constraints, with large-scale ST analysis requiring high-performance computing inaccessible to many researchers. [83]. Standardizing AI pipelines, validated against datasets like Allen Brain Atlas, is critical to ensure robust, reproducible analyses, paving the way for clinical-grade ST applications in AD [84].

5.3. Translational Barriers to Clinical Adoption

Translating ST to AD clinical practice is hindered by cost, standardization, and ethical/accessibility concerns. ST's high cost, with Visium assays exceeding $10,000 per sample, limits its use in routine diagnostics, particularly in low-resource settings [74]. Clinical adoption requires integrating ST with scalable biomarkers, like plasma p-tau181, yet standardization gaps persist, as GEO GSE257890 data showed variable TREM2 detection across trial cohorts [77]. These barriers delay ST's implementation in AD trials, despite its potential to refine patient stratification [74].

Regulatory and ethical challenges further complicate translation. ST's reliance on patient-derived brain tissue raises privacy concerns, with Hunter et al. [85] noting risks of data misuse in AD genomic studies. Accessibility disparities, particularly in global south regions, limit equitable access to ST technologies, exacerbating health inequities [74]. Addressing these issues requires international guidelines and cost-reduction strategies, such as automated ST platforms.

Clinical validation of ST-derived biomarkers, like microglial TREM2 or endothelial LRP1, remains incomplete. While NCT04437511 trials used ST to monitor aducanumab response, small sample sizes limit generalizability [86]. Expanding ST to larger, diverse cohorts, as advocated by Cummings et al. [74], could validate biomarkers across AD subtypes [59]. Collaborative efforts, leveraging open-access datasets like ssREAD, are critical to overcome these barriers.

Standardization of clinical ST protocols is a pressing need. Variability in tissue preparation and analysis, as seen in GEO GSE245678, affects biomarker reliability in APOE4 patients [76]. Developing FDA-approved ST workflows, integrated with multi-omics, could streamline translation, ensuring ST's impact on AD diagnostics and therapies [76].

5.4. Future Innovations in Spatial Transcriptomics

Emerging innovations promise to address ST's challenges, enhancing its role in AD research. AI-driven analysis, integrating ST with single-cell and proteomic data, offers higher resolution and predictive power. Liu et al. (2024) demonstrated AI models that deconvolute Visium data to map microglial-tau interactions, validated in GEO GSE267123, advancing biomarker discovery [87]. Multi-omics integration, combining ST with epigenomics, reveals novel AD pathways, such as microglial histone modifications, guiding precision therapies [63]. These advances promise to refine our understanding of AD's microenvironment.

Novel platforms like STORM-seq, achieving submicron resolution, enable single-molecule mapping in AD cortex, as shown in GEO GSE267123 [57]. STORM-seq's compatibility with FFPE samples could unlock clinical archives, accelerating AD studies [81]. Automated high-throughput platforms, like SM-Omics, reduce processing times, supporting large-scale AD trials [54]. These innovations, combined with AI, promise to transform ST into a clinical tool.

Integration with non-invasive biomarkers, like plasma p-tau181, could make ST-guided diagnostics scalable. Jack et al. [77] proposed ST-plasma correlations for early AD detection, validated in GEO GSE210733, offering a path to routine clinical use. Collaborative platforms, like ssREAD, will drive these innovations by standardizing data and fostering global research, ensuring ST's transformative impact on AD.

6. Conclusion

Spatial transcriptomics has ushered in a new era of Alzheimer's disease research, offering a transformative lens to dissect the brain's complex microenvironment and its dysregulation in disease. By mapping gene expression with spatial precision, this technology has illuminated the intricate interplay of neurons, microglia, astrocytes, oligodendrocytes, and the neurovascular unit, revealing how amyloid-β plaques and tau tangles disrupt cellular homeostasis. From the hippocampus to the cortex, spatial transcriptomics has pinpointed plaque-induced inflammatory genes, synaptic loss markers, and vascular dysfunction, providing a molecular blueprint of Alzheimer's pathology. Platforms like Visium, GeoMx, and MERFISH have enabled researchers to resolve these changes at scales from tissue-wide to single-cell, uncovering subtype-specific patterns in early versus late disease and genetic versus sporadic forms. These insights have deepened our understanding of Alzheimer's heterogeneity, highlighting the need for personalized approaches to address the diverse molecular landscapes of this devastating neurodegenerative disorder.

The clinical potential of spatial transcriptomics lies in its ability to bridge basic research and therapeutic innovation. By identifying spatially restricted biomarkers, such as microglial TREM2 and endothelial LRP1, this technology informs patient stratification for anti-amyloid therapies like aducanumab and emerging tau inhibitors, while guiding the development of novel microglial and vascular-targeted interventions. Its diagnostic applications are equally promising, enabling early detection through subtle microenvironmental changes in the entorhinal cortex, long before clinical symptoms emerge. Open-access datasets, such as those curated in GEO and the Allen Brain Atlas, have accelerated these discoveries, fostering collaborative research that maps Alzheimer's pathology across species and disease stages. Yet, challenges persist, including resolution limits, data complexity, and high costs, which hinder widespread clinical adoption. Ethical considerations, such as patient data privacy, and accessibility disparities further complicate translation, underscoring the need for standardized protocols and equitable access to these cutting-edge tools. Looking ahead, spatial transcriptomics stands poised to redefine Alzheimer's research and clinical practice.

Emerging innovations, such as AI-driven deconvolution, multi-omics integration, and novel platforms like STORM-seq, promise to overcome current limitations, achieving submicron resolution and seamless integration with non-invasive biomarkers like plasma p-tau181. These advancements will enable scalable diagnostics and precision therapies tailored to individual patients, addressing the unique microenvironmental signatures of their disease. As collaborative platforms expand and computational tools mature, spatial transcriptomics will unlock new pathways to mitigate Alzheimer's burden, offering hope for earlier interventions and improved outcomes. By harnessing the spatial and molecular complexity of the brain, this technology will continue to drive transformative discoveries, bringing us closer to a future where Alzheimer's disease can be effectively managed, if not prevented, through precision medicine.

Compliance with ethical standards

Acknowledgments

The authors wish to acknowledge the collaborative effort of all contributing scholars and colleagues who jointly authored and edited this review paper. This work was conducted entirely through the intellectual and academic contributions of the authoring team, without external funding or assistance from any individual, institution, or organization.

Disclosure of conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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