Symposium

Beyond Transcriptomes and Dissociated Cells: Spatial Proteomics for Mechanistic Neurobiology

Timothy C. Orr,[1] Jake S. Boles,[2] Caitlin S. Latimer,[3] Xuehan Sun,[1] Shiva Kazempour Dehkordi,[1] Zhuhao Wu,[4] Lyndsay E. A. Young,[5] Theodore J. Zwang,[6] Dina Hashoul,[6] C. Dirk Keene,[7] and Miranda E. Orr[1,8]

[1]Department of Neurology, Washington University School of Medicine, St. Louis, Missouri 63110, [2]Department of Neurology, Northwestern University, Chicago, Illinois 60611, [3]Department of Laboratory Medicine and Pathology, University of Washington, Seattle, Washington 98195, [4]Department of Neuroscience, Weill Cornell Medical College, New York, New York 10065, [5]Department of Pharmacology and Immunology, Medical University of South Carolina, Charleston, South Carolina 29425, [6]Department of Neurology, Massachusetts General Hospital, Charlestown, Massachusetts 02129, [7]Department of Pathology, University of California San Diego, San Diego, California 92093, and [8]St. Louis VA Medical Center, St. Louis, Missouri 63106

Single-cell transcriptomic studies have revealed remarkable molecular heterogeneity across neuronal and glial populations during development, aging, and disease. However, dissociation-based approaches disrupt tissue architecture, and RNA measures alone incompletely capture cellular function. These limitations are particularly relevant in neurodegenerative diseases, where pathology develops within cellular microenvironments and diseased cells progressively lose canonical cell-state identity markers. Spatial proteomic approaches are beginning to address this critical gap by enabling high-dimensional molecular profiling within the intact tissue, preserving the spatial relationships between vulnerable cells and their surrounding cellular environments across scales ranging from subcellular single-cell imaging to large-volume three-dimensional mapping. Here, we discuss emerging spatial proteomic technologies and their applications in aging and neurodegeneration, emphasizing how integration with complementary modalities, including transcriptomics, glycomics, three-dimensional genome architecture, and quantitative neuropathology, is providing new insight into disease biology. We further highlight how these approaches are beginning to accelerate therapeutic target validation, biomarker discovery, and treatment response monitoring. Realizing the full potential of spatial proteomics will require continued advances in cross-platform harmonization, analytical standardization, and computational methods capable of integrating increasingly complex, multimodal datasets.

Introduction

Modern neuroscience has become remarkably successful at defining cell identity and, increasingly, in linking cellular states to disease mechanism. Single-cell and single-nucleus transcriptomics have been central to this progress. Such studies are revealing extensive cellular heterogeneity across the healthy and diseased nervous system and, when paired with spatial, neuropathological, and genetic manipulation approaches, are establishing causal relationships between specific transcriptional states and pathobiology (Krasemann et al., 2017; Sala Frigerio et al., 2019; Zhou et al., 2020; Johnston et al., 2025). In Alzheimer's disease (AD), Parkinson's disease, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and related disorders, transcriptomic studies identified disease-associated microglia, reactive astrocyte states, oligodendrocyte alterations, and neuronal subtype-specific responses that were previously inaccessible using bulk tissue approaches (Keren-Shaul et al., 2017; Grubman et al., 2019; Maniatis et al., 2019; Mathys et al., 2019; Al-Dalahmah et al., 2020; Zhong et al., 2020; Leng et al., 2021; Gerrits et al., 2022; Kamath et al., 2022; Gabitto et al., 2024). Diseased cells often progressively lose canonical cell-state identity markers, partly owing to genomic instability (Dileep et al., 2023; Traxler et al., 2023), complicating cell classification and interpretation in aging and neurodegenerative disease.

These advances transformed the field, but important limitations remain. Traditional single-cell omics approaches require tissue dissociation, which disrupts spatial organization and erases information on cellular interactions within cellular niches, pathology-associated microenvironments, vascular interfaces, and neuronal circuitry. Spatial transcriptomic technologies have mitigated the loss of anatomical information by preserving molecular measurements within intact tissue sections, revealing how cellular states, pathological features, and neuroimmune interactions are spatially organized across brain regions and disease stage (Chen et al., 2020; Longo et al., 2021; Gabitto et al., 2024; Method of the Year 2020: spatially resolved transcriptomics, 2021).

Messenger RNA abundance incompletely predicts protein abundance, localization, or activity (Vogel and Marcotte, 2012;

Received May 27, 2026; revised Aug. 12, 2026; accepted Aug. 17, 2026.

Author contributions: T.C.O., J.S.B., C.S.L., X.S., S.K.D., Z.W., L.E.A.Y., T.J.Z., D.H., C.D.K., and M.E.O. wrote the paper.

We acknowledge Drs. Rachel E. Bennett, David Gate, and Richard R. Drake for their insightful comments, constructive feedback, and editorial suggestions during manuscript preparation. ChatGPT (OpenAI) was used to assist with the creation and refinement of schematic figures; all figure content was subsequently reviewed, edited, and verified for scientific accuracy by the authors. This work was supported by NIH/NIA T32AG020506 to J.S.B.; NIH/NIA P30AG066509, U19AG060909, and R01AG0909551 to C.S.L.; NIH/NIMH RF1MH128969 and R01MH142410 to Z.W.; Coins for Alzheimer's Research Trust to T.J.Z.; NIH/NIA R01AG078702 to R.R.D.; NIH/NIA R21AG08790703, R01AG085182-01A1, and R01AG06829306; VA Merit 5I01BX005717-02; American Federation for Aging Research; Cure Alzheimer's Fund; Alzheimer's Drug Discovery Foundation; Rainwater Charitable Foundation; and Tracy Family SILQ Center to M.E.O.

The authors declare no competing financial interests.

Correspondence should be addressed to Miranda E. Orr at orr.m@wustl.edu.

https://doi.org/10.1523/JNEUROSCI.1180-26.2026

Copyright © 2026 the authors

Liu et al., 2016; Buccitelli and Selbach, 2020). Many core features of neurodegeneration, including tau phosphorylation, TDP-43 aggregation, complement activation, lysosomal dysfunction, receptor trafficking, and senescence-associated signaling, are fundamentally protein state-dependent processes (Chinta et al., 2018; Musi et al., 2018; Riessland et al., 2019); they cannot be adequately inferred from transcriptomic measurements alone (Hudson et al., 2024). Recent advances in spatial proteomic imaging address these limitations by enabling simultaneous visualization of hundreds to thousands of proteins directly within the intact tissue, preserving cytoarchitecture, neighboring cellular interactions, tissue microenvironments, and pathological context (Goltsev et al., 2018; Gut et al., 2018; Merritt et al., 2020; Hickey et al., 2022).

Spatial proteomics is increasingly being integrated with orthogonal modalities including spatial transcriptomics, glycomics, 3D genome architecture, and neuropathology, enabling a more comprehensive understanding of tissue physiology and disease biology across molecular and anatomical scales. Collectively, these developments extend this trajectory: building on transcriptomic and functional studies that have already linked cellular states to mechanism, spatial proteomics adds a protein-level, spatially resolved dimension to resolving dynamic cellular states within spatially organized tissue microenvironments. Realizing this potential will require computational approaches that keep pace with the scale and complexity of spatial protein data, moving beyond methods built for transcriptomic or single-modality analyses toward strategies capable of integrating high-dimensional, multiscale protein measurements directly within their spatial context. Spatial proteomics is therefore emerging not simply as a technological advance but as a foundational approach for mechanistic neurobiology that links molecular pathways to tissue architecture, selective vulnerability, disease progression, biomarker discovery, therapeutic response, and ultimately translational neuroscience (Fig. 1).

Why Protein Biology Matters for Neurodegeneration

A central challenge in neurodegeneration is distinguishing disease-associated changes that may contribute to pathology from those that arise as downstream consequences. Transcriptomic studies have transformed our understanding of gene regulation, cell identity, and cellular heterogeneity (Hodge et al., 2019; Network, 2021; Yao et al., 2021, 2023; Siletti et al., 2023), but transcript abundance often incompletely reflects protein abundance, localization, activity, or signaling state (Buccitelli and Selbach, 2020; Wang et al., 2025). Consequently, many biologically relevant processes occur downstream of transcription, and capturing them requires direct protein- or translation-level measurement: layers of information otherwise invisible to transcriptomic and genetic readouts (Vogel and Marcotte, 2012; Liu et al., 2016; Buccitelli and Selbach, 2020; Koch et al., 2026). Spatial proteomics, particularly when integrated with complementary molecular and neuropathological measurements, can help establish the cellular and anatomical context of these protein changes and prioritize candidates for subsequent mechanistic investigation.

Proteomic approaches capture multiple dimensions of protein biology, including abundance, posttranslational modifications, proteolytic cleavage, conformation, subcellular localization, turnover, and clearance (Larance and Lamond, 2015; Aebersold and Mann, 2016). These measurements have been fundamental to understanding the molecular mechanisms underlying neurodegenerative disease. In prion disorders, pathogenic protein conformations and templated misfolding drive neurodegeneration despite relatively limited changes in gene expression (Chesebro et al., 1985; Caughey et al., 1988; Brundin et al., 2010). In AD

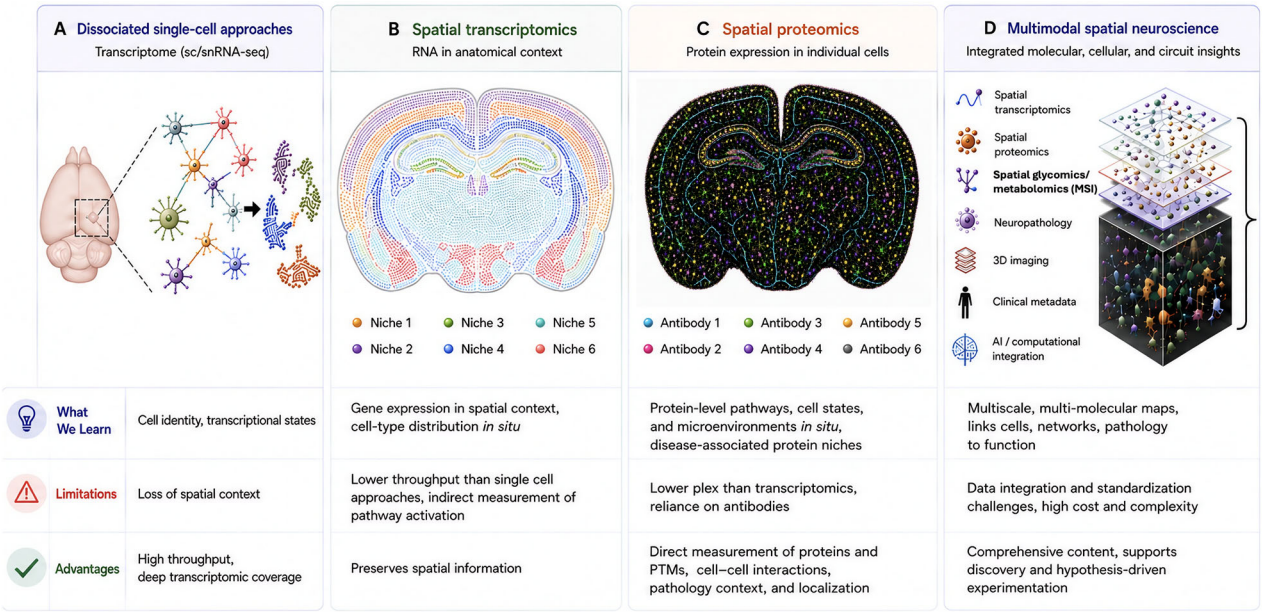


Figure 1. Spatial proteomics bridges molecular profiling and intact tissue biology. ***A***, Dissociation-based single-cell and single-nucleus transcriptomic approaches transformed molecular classification of nervous system cell types but disrupt spatial organization and incompletely capture protein-level biology. ***B***, Spatial transcriptomics preserves anatomical context while enabling localization of gene expression patterns, cell-type distributions, and molecular niches within intact tissue; however, transcript abundance does not fully predict protein abundance, localization, posttranslational modification, or pathway activation. ***C***, High-plex spatial proteomic imaging extends molecular neuroscience by directly localizing protein pathways, cellular states, and pathology-associated microenvironments in situ, including protein abundance, posttranslational modifications, and cell–cell interactions. ***D***, Emerging multimodal approaches integrate spatial transcriptomics and proteomics with imaging mass spectrometry–based glycomics, lipidomics, and metabolomics, neuropathology, three-dimensional imaging, clinical metadata, and computational analysis to generate multiscale, multimolecular maps linking cells, networks, and pathology to function, supporting both discovery and hypothesis-driven experimentation.

and primary tauopathies, protein phosphorylation, truncation, aggregation state, and subcellular localization shape pathogenicity and help distinguish one tauopathy from another (Hyman et al., 2012; Wang and Mandelkow, 2016). In Parkinson's disease, the accumulation and propagation of misfolded α-synuclein are associated with widespread alterations in vesicular trafficking, lysosomal function, mitochondrial biology, and neuroimmune signaling (Spillantini et al., 1997; Rocha et al., 2018). Likewise, in ALS and FTD, TDP-43 pathology disrupts RNA processing, nucleocytoplasmic transport, and proteostasis in ways that generate substantial discordance between transcriptomic and proteomic states (Ling et al., 2013, 2015). Huntington's disease similarly involves complex alterations in protein aggregation, synaptic signaling, metabolism, and selective neuronal vulnerability that extend beyond transcriptional regulation alone (Ross and Tabrizi, 2011; Bates et al., 2015).

Neurodegenerative diseases also exhibit substantial neuropathological heterogeneity. For example, α-synuclein and TDP-43 frequently occur as secondary pathologies in AD, suggesting that comorbid protein changes may arise downstream of primary disease processes (Robinson et al., 2023). These disease-associated changes extend across cell types, with recent studies implicating microglia, astrocytes, vascular cells, and other cellular populations in neurodegenerative disease biology (De Strooper and Karran, 2016; Keren-Shaul et al., 2017; Habib et al., 2020; Sun et al., 2023). Importantly, many of these protein-level responses are highly localized within specific tissue microenvironments. Recent studies have identified pathology-associated cellular niches characterized by coordinated alterations in complement signaling, lysosomal pathways, inflammatory mediators, metabolic programs, and extracellular communication (Walker et al., 2022, 2024; Richardson et al., 2025). These localized responses may not be fully predicted from transcriptional profiles alone, highlighting the value of preserving native spatial context during molecular measurement.

Many disease-modifying therapies ultimately target protein state, making direct protein measurements essential for evaluating target engagement and biological response, as discussed in the "Translational Implications" section. Beyond assessing therapeutic effects, protein measurements also serve as important biomarkers of disease state and progression. Particularly informative biomarkers capture disease-associated proteoforms or posttranslational modifications, making their identification and validation important areas of investigation. For example, therapies have relied on monitoring amyloid, SOD1, huntingtin, progranulin, phosphorylated LRRK2, and phosphorylated Rab10 to establish target engagement independently of clinical change (Tabrizi et al., 2019; Jennings et al., 2022; Miller et al., 2022; Kurnellas et al., 2023; Sims et al., 2023). More recently, phosphorylated tau species in plasma have become central to staging and trial enrichment for AD. pTau217 abundance in plasma is closely associated with amyloid pathology (Palmqvist et al., 2020). Plasma MTBR-tau243 specifically reflects tau tangle pathology and correlates strongly with tau PET (Horie et al., 2025). Continued identification of disease-associated proteins in plasma and CSF may yield additional biomarkers with diagnostic, prognostic, or pharmacodynamic value (Ali et al., 2026). Ultimately, understanding which cell types, brain regions, and pathological microenvironments give rise to proteins detected in plasma and CSF will be essential for linking fluid biomarkers to disease mechanisms.

Together, these considerations underscore the need to measure protein biology within its native tissue context. Spatial proteomics can localize disease-associated proteomic states to specific cell types and pathological features while preserving their relationships to surrounding tissue architecture. In this way, spatial proteomics complements transcriptomic and other molecular approaches by linking protein state with cellular identity, anatomical context, and quantitative neuropathology.

Spatial Organization of Pathology and Cellular States

A defining feature of the nervous system is its spatial organization. Neuronal function depends on precise anatomical relationships spanning synapses, local circuits, laminar structures, and long-range projections. Likewise, neurodegenerative diseases arise within selective, disease-specific brain regions and progress through anatomically interconnected networks as pathology advances (Braak and Braak, 1991; Nelson et al., 2019). Emerging spatial profiling technologies are revealing that these pathological processes unfold within highly organized microenvironments shaped by neighboring cells, extracellular matrix composition, vascular interactions, and region-specific vulnerability (Fig. 2).

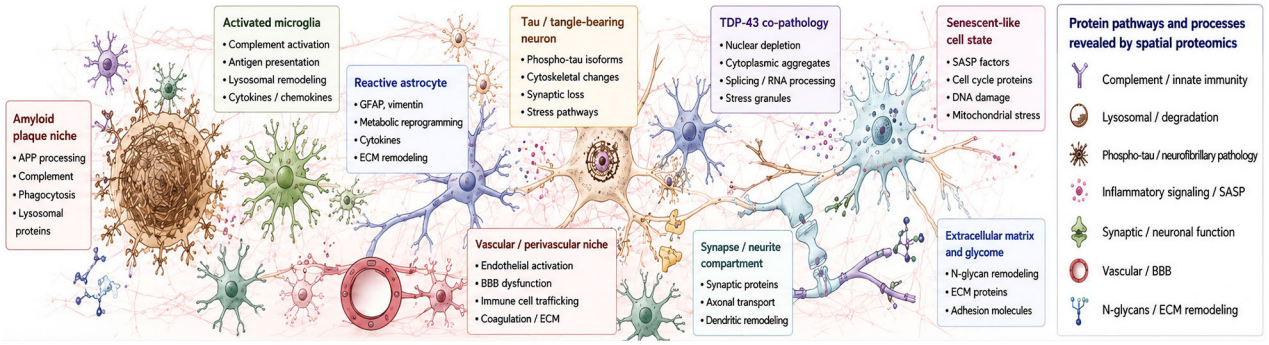


Figure 2. Spatial proteomics characterizes molecular features of pathology-associated microenvironments. Neurodegenerative pathology is spatially organized within highly structured cellular niches composed of neurons, glia, vasculature, extracellular matrix, and pathology-associated protein aggregates. Spatial proteomic approaches enable localization of protein pathways within amyloid plaque niches, tau/tangle-bearing neurons, TDP-43 copathology, reactive astrocytes, activated microglia, vascular/perivascular compartments, synaptic regions, extracellular matrix remodeling zones, and senescent-like cellular states. These microenvironments exhibit coordinated alterations in complement activation, lysosomal remodeling, protein accumulation, inflammatory signaling, synaptic dysfunction, vascular injury, extracellular matrix remodeling, and senescence-associated secretory pathways. Integration of protein-level measurements with transcriptomics, imaging mass spectrometry–based glycomics, lipidomics, and metabolomics, imaging, and neuropathology can define molecular features associated with selective vulnerability, resilience, and disease progression and generate mechanistic hypotheses for subsequent experimental validation.

Spatial imaging studies increasingly demonstrate that pathology-associated cellular states are not randomly distributed but instead cluster within discrete molecular niches. In AD, amyloid plaques are surrounded by highly organized glial microenvironments containing activated microglia, reactive astrocytes, dystrophic neurites, and altered extracellular signaling molecules (Duyckaerts et al., 2009; Prokop et al., 2019; Bathe et al., 2024; Tsering and Prokop, 2024). These plaque-associated niches exhibit coordinated protein-level alterations involving complement activation, lysosomal pathways, inflammatory signaling, and synaptic remodeling. Importantly, the composition of these microenvironments varies substantially across disease stages and brain regions, suggesting dynamic spatial regulation of neuroimmune responses (Leng and Edison, 2021; Fruhwurth et al., 2024).

Tau pathology likewise appears closely linked to local circuit organization and selective neuronal vulnerability across both AD and primary tauopathies. Importantly, the spatial organization of tau pathology differs substantially across tauopathies. Whereas AD is characterized by mixed 3R/4R tau aggregates that follow a stereotyped neuroanatomical progression, primary tauopathies such as progressive supranuclear palsy, corticobasal degeneration, Pick's disease, and aging-related tau astrogliopathy (ARTAG) exhibit distinct cellular, regional, and network-level distributions (Dickson, 2009; Kovacs et al., 2016). These disorders differ not only in the neuronal and glial populations affected but also in the molecular composition and morphology of tau inclusions themselves. Spatial proteomic approaches therefore provide an opportunity to define disease-specific microenvironments associated with neuronal tangles, astrocytic plaques, tufted astrocytes, coiled bodies, and other tau lesions, potentially revealing mechanisms that drive selective regional vulnerability across clinically and pathologically distinct tauopathies. These approaches integrated with spatial transcriptomics, imaging mass spectrometry, and laser-capture methodologies have begun to identify molecular features associated with neurofibrillary tangle-bearing neurons, including altered stress–response pathways, cytoskeletal remodeling, impaired proteostasis, and loss of canonical neuronal identity markers (Drummond et al., 2015; Hondius et al., 2021; Otero-Garcia et al., 2022; Walker et al., 2022, 2024; Richardson et al., 2025; Foiani et al., 2026; Thierry et al., 2026).

Emerging evidence further suggests that neurons containing mature neurofibrillary tangles may persist longer than previously appreciated and may exhibit distinct molecular programs compared with neurons harboring soluble or pretangle tau species (de Calignon et al., 2009; Zwang et al., 2024). These findings challenge traditional assumptions regarding tau-mediated neurotoxicity and raise important questions about neuronal resilience, adaptive cellular states, and compensatory remodeling within pathological environments, suggesting that tangle formation may, in some contexts, represent a relatively stable cellular state rather than an immediate precursor to neuronal death (Zwang et al., 2024). This concept is consistent with emerging evidence that tau-bearing neurons can adopt a senescence-like state characterized by persistent stress signaling, altered metabolic and transcriptional programs, and long-term survival despite substantial cellular dysfunction (Musi et al., 2018; Dehkordi et al., 2021).

Similar principles are emerging across other neurodegenerative proteinopathies. In PD and related synucleinopathies, α-synuclein pathology is associated with regionally organized microglial activation, mitochondrial dysfunction, disrupted vesicular trafficking, and selective vulnerability of dopaminergic neurons and interconnected neural circuits (Surmeier et al., 2017; Coukos and Krainc, 2024; Kampmann, 2024; Ma et al., 2025). In ALS and FTD, TDP-43 pathology exhibits strong spatial relationships with neuronal subtype vulnerability, glial activation states, and white matter-associated inflammatory responses (Neumann et al., 2006; Maniatis et al., 2019). TDP-43 pathology also contributes to cognitive impairment in aging independent of ALS/FTLD-TDP; limbic-predominant age-related TDP-43 encephalopathy (LATE-NC) follows a stereotyped progression through the amygdala, hippocampus, and medial frontal cortex, frequently co-occurring with AD and other age-related pathologies (Nelson et al., 2019). Spatially resolved approaches are well suited to characterize these TDP-43 microenvironments, distinguish cell-autonomous from non-cell–autonomous responses, and identify regional factors underlying selective vulnerability within limbic and neocortical networks.

Vascular pathology represents a distinct and highly relevant contributor to age-related neurodegeneration and cognitive impairment. Cerebral small vessel disease, including arteriolosclerosis, microinfarcts, perivascular space enlargement, and blood–brain barrier dysfunction, is among the most common age-related pathologies affecting the brain (Blevins et al., 2021). Growing evidence suggests that vascular injury may influence regional vulnerability and clinical resilience through effects on cerebral perfusion, blood–brain barrier integrity, neurovascular coupling, perivascular protein clearance, and neuroimmune signaling (Sweeney et al., 2019). The neurovascular unit itself constitutes a highly organized spatial niche composed of endothelial cells, mural cells, astrocytic end feet, perivascular immune cells, and extracellular matrix components (Schaeffer and Iadecola, 2021). Spatial proteomic approaches are uniquely positioned to characterize these vessel-centered microenvironments and define how vascular dysfunction contributes to selective regional vulnerability, neuronal injury, and cognitive impairment within aging brain networks.

Copathologies further complicate these spatial landscapes as mixed pathology represents the rule rather than the exception in late-life neurodegenerative disease (Kapasi et al., 2017; Boyle et al., 2019). AD neuropathologic change frequently coexists with LATE-NC, Lewy body disease, cerebrovascular pathology, ARTAG, argyrophilic grain disease, and other age-related pathologies. These lesions often occupy overlapping anatomical territories while contributing differentially to clinical phenotypes. Spatially resolved proteomic approaches provide an important framework for disentangling these interacting pathologies by simultaneously characterizing lesion-specific molecular signatures and the surrounding cellular responses within shared tissue environments (Fig. 2). In one case, spatial proteomic profiling of an individual harboring both Down syndrome and a pathogenic PSEN2 variant revealed markedly increased amyloid burden without corresponding increases in tau pathology or neuroinflammatory markers (Ogg et al., 2025), illustrating how spatially resolved approaches can help disentangle convergent and divergent disease mechanisms in individual cases of mixed pathology.

Beyond pathology-associated microenvironments, spatial proteomics is also illuminating broader principles of cellular organization across the nervous system. High-dimensional brain atlasing efforts combined with AI-assisted annotation are beginning to generate reproducible spatial references capable of linking molecular states to anatomical and functional organization across scales as discussed below. Integrating these references with disease-associated molecular profiles may clarify how pathology reshapes tissue organization, circuit function, and cellular communication, ultimately refining neuropathological classification, disease staging, and therapeutic development.

Emerging Spatial Proteomic Technologies and Analytical Strategies

Rapid technological innovation has substantially expanded the capabilities of spatial imaging. Current approaches span a wide range of spatial scales, molecular targets, and analytical strategies, each optimized for distinct biological questions (Fig. 3). Highly multiplexed single-cell imaging platforms enable simultaneous visualization of dozens to hundreds of proteins within intact tissue sections (Gerdes et al., 2013; Angelo et al., 2014; Lin et al., 2015; Murray et al., 2015; Agasti et al., 2017; Goltsev et al., 2018; Keren et al., 2018; Saka et al., 2019; Jackson et al., 2020; Radtke et al., 2020; Hosogane et al., 2023; Hong et al., 2024; Walker et al., 2022, 2024; Richardson et al., 2025). These approaches preserve cellular morphology and spatial relationships while permitting detailed characterization of neuronal, glial, vascular, and immune states. Their integration with pathology markers allows direct correlation between molecular pathways and neuropathological features.

Multiplexed immunostaining platforms, including PhenoCycler-Fusion (formerly CODEX) and CellScape (Bruker), have enabled high-dimensional characterization of cellular interactions within the AD tissue. For example, analysis of microglia in proximity to amyloid-β plaques revealed a shift toward a macrophage-like activation state (Sanchez-Molina et al., 2026). Similarly, multiplexed ion beam imaging (Angelo et al., 2014) has characterized the molecular architecture of the amyloid plaque niche, identifying AD-specific microglial interactions with pathology (Vijayaragavan et al., 2022) and protein signatures consistent with microglial immune exhaustion (Mrdjen et al., 2025).

Rather than resolving every cell within a tissue section, region-of-interest (ROI)-based approaches prioritize molecular depth within biologically defined anatomical compartments, providing complementary information to whole-slide single-cell imaging platforms. For example, the GeoMx DSP combines spatially resolved profiling with highly multiplexed RNA and protein measurements that are compatible with the intact archival formalin-fixed paraffin-embedded (FFPE) tissue (Merritt et al., 2020). Fluorescent morphology markers define ROIs for quantitative profiling of the whole transcriptome and/or hundreds of protein targets using UV-photocleavable barcodes (Sun et al., 2025; Tan et al., 2025). Although ROI-based approaches lack whole-slide single-cell resolution, they provide substantially greater molecular depth and robust quantification across predefined tissue compartments, making them particularly well suited for cohort-scale mechanistic studies (Prokop et al., 2019; Walker et al., 2022, 2024; Richardson et al., 2025). Applied across cohorts of AD, primary age-related tauopathy (PART), and chronic traumatic encephalopathy (CTE), these studies demonstrated that hippocampal neurons resilient to tau pathology reside within distinct neuroimmune microenvironments compared with vulnerable neurons from patients with dementia (Walker et al., 2022, 2024; Richardson et al., 2025). They further revealed that Aβ status, rather than tau burden alone, is a major determinant of the neuronal proteome, with Aβ-independent tauopathies (PART and CTE) sharing proteomic signatures that differ markedly from Aβ-positive disease states. Similarly, digital spatial profiling has been used to define the protein and transcriptomic signatures of distinct amyloid plaque subtypes and the surrounding neuronal and glial responses associated with each plaque niche (Tsering et al., 2023). The reproducibility,

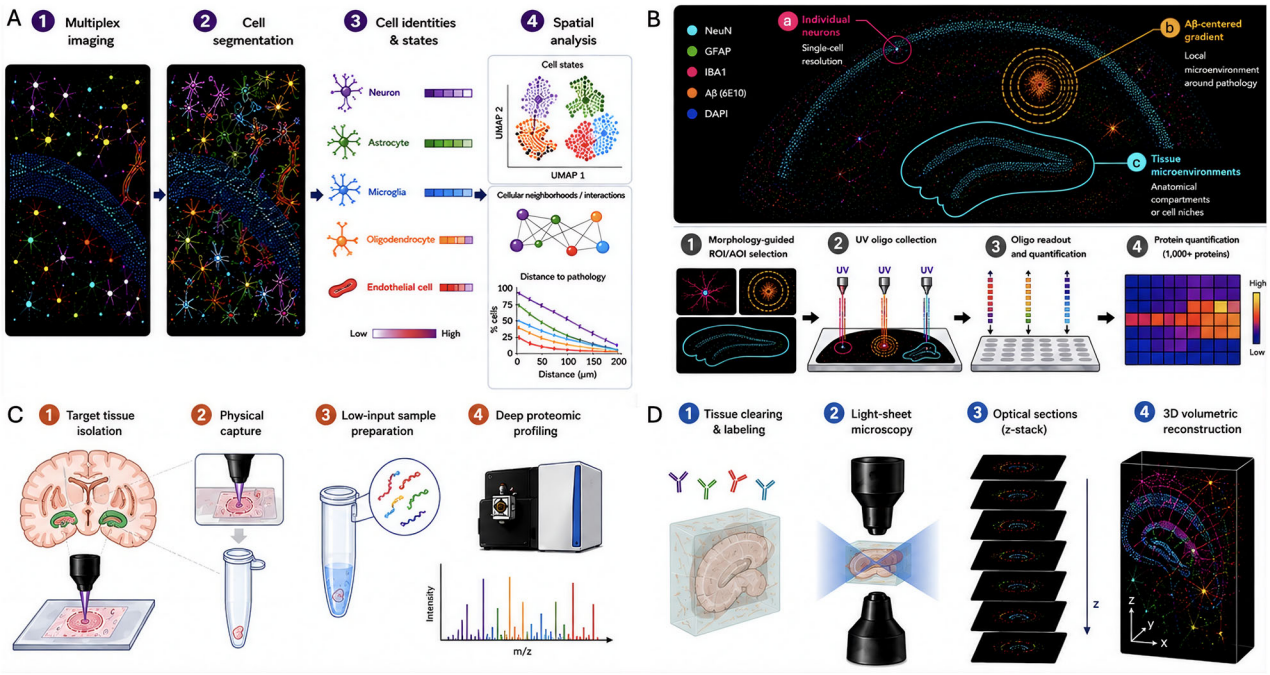


Figure 3. Matching spatial proteomic strategies to biological questions. Spatial proteomic approaches provide complementary strengths in spatial resolution, molecular depth, and throughput. ***A***, Multiplexed immunofluorescence enables subcellular-to-tissue-scale visualization of tens to hundreds of proteins with high imaging throughput. ***B***, ROI-based spatial proteomics enables targeted profiling of individual cells, pathological features, or multicellular anatomical regions, measuring hundreds to thousands of predefined proteins with high throughput. ***C***, LCM coupled with mass spectrometry enables targeted isolation of individual cells, cell populations, pathological structures, or anatomical regions for deep, untargeted proteomic profiling of hundreds to thousands of proteins, although at lower throughput. ***D***, Tissue clearing and three-dimensional imaging enable cellular-to-organ-scale visualization of molecular and cellular organization across large tissue volumes, with comparatively lower molecular depth using targeted antibody panels and lower sample throughput. Technology selection should therefore be guided by the biological question, required spatial resolution and coverage, molecular depth, throughput, tissue availability, and translational objective. ROI, region of interest; AOI, area of illumination.

molecular depth, and compatibility of ROI-based approaches with the archival FFPE tissue make them particularly well suited for large cohort studies linking spatial molecular signatures with clinicopathological phenotypes.

Other strategies, including laser-capture microdissection (LCM) and laser-guided biotinylation, further enable targeted isolation of individual pathological structures or vulnerable cell populations with unbiased downstream proteomics or transcriptomics. LCM extracts small amounts of the tissue from a section, guided by a fluorescent signal. LCM has been used to identify the proteome of amyloid plaques and neurofibrillary tangles (Drummond et al., 2015, 2018; Nijholt et al., 2015), nominating nonamyloid therapeutic targets and revealing how the tangle proteome itself is remodeled across disease stages, from PART through advanced AD. LCM has also been used to build the transcriptomes of dopaminergic neurons in the PD brain, finding gene signatures associated with dysfunctional metabolism and elevated expression of alpha-synuclein (Grundemann et al., 2011), providing insight on a neuronal population that is difficult to study in the human brain. LCM-based proteomics has similarly informed understanding of other neurodegenerative proteinopathies: unbiased proteomic profiling of cortical Lewy bodies has identified novel constituent proteins beyond the core α-synuclein aggregate (Leverenz et al., 2007), and single-neuron proteomic profiling of postmortem spinal motor neurons in ALS, stratified by TDP-43 inclusion status, has revealed disease-associated reductions in oxidative phosphorylation, RNA splicing, and vesicular transport proteins (Guise et al., 2024). A successor platform to LCM, laser-guided biotinylation, uses two-photon excitation of a cleavable biotinylation reagent guided by fluorescent microscopy; this technique has identified binding partners for the NLRP3 inflammasome during macrophage activation in vitro (Y. Zhang et al., 2026). Its application in neuroscience is still young, but the unbiased characterization of proteomes in cells with pathogenic protein inclusions, spatially defined vulnerable neuronal populations, and microglial phagosomes in disease, for example, will be highly fruitful endeavors.

Emerging three-dimensional spatial proteomic approaches are beginning to extend these capabilities beyond individual tissue sections (Chung et al., 2013; Ueda et al., 2020a). Three-dimensional imaging permits reconstruction of molecular organization across larger anatomical volumes, potentially enabling investigation of pathology propagation, circuit vulnerability, and neuroimmune organization across connected brain regions (Ueda et al., 2020b). More broadly, recent large-scale spatial atlasing efforts have demonstrated the power of combining whole-brain imaging, computational registration, and machine learning–based analyses to generate cellular-resolution maps of brain organization (Murakami et al., 2018; Kronman et al., 2024; Park et al., 2024). For example, comprehensive three-dimensional atlases of cell-type density patterns reveal that distinct neuronal and glial populations exhibit highly stereotyped spatial distributions that closely align with anatomical boundaries and functional brain systems (Liwang et al., 2025; Zhao et al., 2025; Liu et al., 2026b). These studies highlight how spatial datasets can move beyond molecular characterization alone to define fundamental organizational principles of the nervous system across multiple spatial scales (Munoz-Castaneda et al., 2025).

Importantly, no single technology currently resolves all relevant biological scales simultaneously. While volumetric labeling and imaging of large brain volume promises comprehensive profiling and organ-level discovery, it also brings rising challenges of scalability and affordability, across each step from sourcing secure reagents to performing effective analysis. In practice, high-resolution single-cell imaging often sacrifices proteomic depth or tissue volume, whereas larger-scale approaches may reduce cellular resolution. Consequently, multimodal and cross-platform integration are becoming increasingly important analytical strategies. These complementary technologies, especially when leveraged in tandem, are optimized for distinct mechanistic questions.

This conceptual shift, from platform-centered comparisons toward question-centered experimental design, will likely become increasingly important as the tools and resources in spatial biology matures (Fig. 3). Careful alignment of biological hypotheses with spatial scale, molecular resolution, tissue preservation, and analytical requirements is essential for generating interpretable and reproducible findings.

Beyond RNA and Protein: Multimodal Spatial Integration

Although transcriptomic and proteomic integration has become a central focus in spatial biology (He et al., 2022), the molecular complexity of neurodegenerative disease extends far beyond these modalities alone. Increasingly, studies are incorporating additional molecular layers including glycomics, lipidomics, metabolomics, and epigenomic information to generate more comprehensive models of disease biology. Mass spectrometry imaging (MSI) enables direct spatial analysis of multiple analytes in the frozen and fixed tissue and has become a powerful tool for multiomic profiling within a single tissue section (Dunne et al., 2023; Vicari et al., 2024), with matrix-assisted laser desorption/ionization MSI (MALDI-MSI) emerging as one of the primary approaches in neurological research given its capacity for sequential, multianalyte analysis on the same slide (Jha et al., 2024).

Brain tissues have the second highest level of lipid content after adipose tissues, and alterations in their levels and composition are associated with many types of neurological diseases (Yoon et al., 2022). The abundance of phospholipids and glycosphingolipids (e.g., gangliosides and sulfatides) present in the brain can be readily detected by MALDI-MSI at cellular and near-cellular resolution in animal model and human tissues (Jha et al., 2024). Beyond lipids, the field has expanded to metabolite profiling, enabling 3D reconstruction for molecular mapping and drug compound imaging, which provides biological context when multiplexed with spatial transcriptomics (Vallianatou et al., 2024; Vicari et al., 2024; Clarke et al., 2025).

Spatial glycomics is emerging as a particularly important dimension in neuroscience, as *N*-glycosylation profoundly influences protein folding, receptor trafficking, immune signaling, and extracellular interactions (Schjoldager et al., 2020). The *N*-glycome of the brain is quite distinct from all other major organs (Wallace et al., 2024), and like for lipids, their abundance and composition are altered in neurological diseases. MALDI-MSI studies have revealed distinct and dysregulated *N*-glycan signatures within pathology-associated regions of both human and mouse tissues, suggesting that alterations in glycosylation may underpin AD pathologies (Hawkinson et al., 2022). A recent multiomic study integrating MALDI-MSI–based metabolomics, lipidomics, and glycomics identified brain hyperglycosylation driven by increased *N*-glycan biosynthesis as a pathological driver of AD; genetic reduction of glycan biosynthetic enzymes improved cognitive outcomes while glucosamine supplementation worsened them (Hawkinson et al., 2026). Beyond neurodegeneration, spatial glycomics has revealed distinct *N*-glycan landscapes in the normal and malignant brain

tissue (Angerstein et al., 2025), with *N*-glycosylation emerging as one of the strongest molecular classifiers of tumor grade across adult and pediatric gliomas (Piyadasa et al., 2026). Together, these studies demonstrate that integrating spatial glycomics with lipidomics, metabolomics, proteomics, and transcriptomics can reveal molecular mechanisms and tissue heterogeneity that remain inaccessible to any single modality alone.

Spatial epigenomic technologies represent another rapidly emerging dimension of multimodal neuroscience by linking genome architecture to cellular state within the intact tissue. Beyond gene expression and protein abundance, the three-dimensional organization of the genome influences transcriptional regulation, cell identity, cell-state transitions, and disease susceptibility. Most chromosome conformation capture technologies, such as Hi-C, rely on proximity ligation (Lieberman-Aiden et al., 2009; Belton et al., 2012; de Laat and Dekker, 2012). Chromatin interactions are first preserved by cross-linking, after which the DNA is digested and religated. Sequencing these ligation products reveals both their genomic origins and their physical proximity within the 3D genome. However, these methods are limited to detecting DNA fragments that are sufficiently close to undergo ligation, and they primarily capture pairwise interactions. SPRITE (Split-Pool Recognition of Interactions by Tag Extension) is a proximity ligation-independent alternative that can reveal higher-order chromatin interactions beyond pairwise contacts (Quinodoz et al., 2022). Although these approaches have been applied, or proposed for application, to tissue-derived cells or nuclei (Arrastia et al., 2022; Meng et al., 2023), they require tissue dissociation or nuclei isolation and therefore do not preserve native tissue architecture.

Alternatively, microscopy-based in situ imaging of genomic loci is inherently compatible with intact tissue. Recent advances have paired multiplexed fluorescence in situ hybridization (FISH) with barcoding strategies, enabling genome-wide coverage, tracing, and reconstruction. For example, DNA seqFISH+ simultaneously maps the spatial arrangement of >3,000 DNA loci in tissue samples (Takei et al., 2021a,b). The PaintScape platform uses jebFISH, also a highly multiplexed in situ genome-labeling technology, to directly visualize and reconstruct genome architecture at single-cell resolution in the intact tissue. This, and other, technologies provide opportunities to investigate how aging, neurodegeneration, and pathological stress reshape nuclear organization across vulnerable neuronal and glial populations (Liu et al., 2026a). Integration of spatial epigenomic measurements with transcriptomic and proteomic datasets may ultimately reveal regulatory mechanisms that precede or drive downstream molecular and pathological changes.

Computational approaches are likewise becoming central to multimodal interpretation. AI-assisted annotation, atlas construction, and spatial harmonization are enabling increasingly scalable and reproducible analyses across datasets and institutions. As spatial datasets continue to increase in dimensionality and complexity, the central challenge is no longer simply generating multimodal data but aligning and interpreting these complementary layers within a shared tissue framework. This is particularly important because spatial modalities differ in resolution, feature space, tissue coverage, and biological scale.

Compounding this challenge, cross-platform and cross-batch harmonization remains a distinct and only partially resolved problem. Differences in panel composition, capture sensitivity, spatial resolution, and sparsity mean that datasets generated across spatial platforms may share only a limited fraction of directly comparable features. In addition, variation introduced by donor characteristics, tissue processing, imaging, and instrument can confound biological signal if not explicitly modeled. Graph-based alignment methods have begun to address this by jointly modeling spatial structure and batch-invariant embeddings, and cross-modal frameworks built on variational autoencoders have extended similar principles to jointly harmonize and fuse molecularly distinct layers (Haber et al., 2025; Tian et al., 2025). A related challenge arises when datasets share only partially overlapping modalities across sections, for which tools such as SpaMosaic have been developed to construct a modality-agnostic, batch-corrected latent space. Beyond aligning shared features, this approach can also impute entirely missing modalities within a section, recovering biologically meaningful cross-modal relationships even without direct coprofiling (Yan et al., 2026). However, recent benchmarking efforts suggest that methods that preserve spatial architecture do not always fully correct strong batch effects, highlighting cross-platform harmonization as an important open challenge for the field (Luecken et al., 2022; Dong et al., 2025; Hu et al., 2025).

Beyond harmonization, recent methods are beginning to address cross-modal fusion through graph-based representation learning and attention-based mechanisms that jointly model spatial proximity, molecular similarity, and biologically defined relationships among cells and tissue structures (Long et al., 2024; Gao et al., 2025; Yan et al., 2026). Conceptually, these approaches build on hierarchical graph strategies developed in digital pathology, where cells, tissue regions, and their spatial relationships can be represented as connected components of a tissue graph (Pati et al., 2022), and extend this logic toward multimodal molecular integration. In this framework, cells, tissue regions, and pathological structures such as plaques, tangles, and vessels can be represented within a shared spatial graph alongside transcript, protein, lipid, glycan, and metabolite measurements. Importantly, these approaches can estimate which modality or spatial relationship contributes most strongly to a given disease-associated state, allowing spatial AI to move beyond classification toward mechanistic interpretation.

Collectively, these developments indicate that the future of spatial biology lies not within any individual modality but rather within integrative frameworks capable of combining complementary molecular and anatomical information into unified mechanistic models.

Translational Implications

Spatial proteomics has important implications for translational neuroscience because it directly links molecular pathways to the cellular, pathological, and anatomical contexts in which disease occurs. This capability enables more precise identification of therapeutic targets, evaluation of target engagement, interpretation of biomarkers, and mechanistic understanding of disease.

One major translational opportunity involves identifying molecular signatures associated with selective vulnerability or resilience. Spatially resolved analyses may reveal why specific neuronal populations degenerate while neighboring cells remain relatively preserved despite similar pathological burden. This principle has already been demonstrated in neurons harboring pathogenic tau across multiple tauopathies, including AD, CTE, and PART, as well as in resilient aging (Walker et al., 2022, 2024; Richardson et al., 2025). A recent study employing spatial proteogenomics identified inflammatory mediators localized to spinal motor neurons with TDP-43 pathology and TDP-43–dependent missplicing in ALS (Z. Zhang et al.,

2026b), and in-progress efforts are approaching a similar spatially resolved understanding of neuronal vulnerability in the ALS/FTD brain (Ruf et al., 2026). Similarly, spatial proteomic analysis of the human AD brain identified disease-associated microglial states defined by their local tissue microenvironment and spatial relationships to Aβ pathology, demonstrating that cellular identity is shaped not only by protein expression but also by spatial context (Sanchez-Molina et al., 2026). These insights could ultimately guide therapeutic strategies aimed at enhancing cellular resilience or interrupting pathological signaling within vulnerable microenvironments.

Spatial proteomics has potential to improve therapeutic target validation by determining whether candidate pathways are truly localized to disease-relevant cell populations and anatomical regions. Similarly, spatial analyses can provide critical information regarding therapeutic target engagement within intact tissue environments, particularly for interventions aimed at modifying neuroimmune signaling, proteostasis, or pathological protein aggregation. For example, a recent multimodal spatial profiling study identified microglial programs associated with amyloid clearance after anti-Aβ immunotherapy, revealing molecular pathways driving the removal of pathological protein aggregates while distinguishing potentially beneficial from maladaptive neuroimmune activation states (van Olst et al., 2025). This study, complemented by similar spatial transcriptomic and in vitro assays (Albertini et al., 2026), characterizes the activation of a neuroimmune program in microglia that is unique to immunotherapy-treated AD. Together, these studies demonstrate how spatially resolved analyses can directly inform therapeutic target prioritization, target engagement, and mechanistic evaluation in human neurodegenerative disease.

In addition, spatial molecular profiling may improve biomarker discovery by identifying tissue-derived signatures associated with specific pathological states. Several biomarkers for neurodegenerative diseases have been used to identify and track disease, including phosphorylated tau species and Aβ peptides in AD (Bateman et al., 2019; Barthelemy et al., 2023; Gonzalez-Ortiz et al., 2023) and misspliced protein products in ALS/FTD (Irwin et al., 2024), but from where these molecules arise in the brain is unknown. Spatial biology approaches can identify the cells, pathological structures, and tissue microenvironments that give rise to these biomarkers, providing mechanistic context for their appearance in plasma and CSF. Alternatively, a growing number of studies highlight cellular dysfunction in the CSF and blood in neurodegeneration, including clonally expanded T cells in AD CSF (Gate et al., 2020), T cells reactive to α-synuclein in PD CSF (Gate et al., 2021), genotype-dependent blood monocyte activation in AD (Ramakrishnan et al., 2024), and inflammatory CSF monocyte and T-cell programs that relate to pathological aging (Piehl et al., 2022), emphasizing potential immune contributors to disease. Spatial biology approaches will link this immune function to brain health, cementing these fluid cells as key actors in disease and bolstering their utility as fluid biomarkers. Integrating these findings with biofluid biomarkers and imaging modalities may ultimately support more precise disease classification and staging.

Importantly, the human tissue remains central to these translational efforts. While experimental models provide critical mechanistic insights, human spatial proteomics enables direct interrogation of disease-relevant biology within the complex pathological environments that characterize aging and neurodegeneration. Because many spatial proteomic platforms are compatible with the standard FFPE tissue, this work can draw directly on existing brain bank collections rather than requiring specially preserved fresh-frozen specimens (Prokop et al., 2019; Walker et al., 2022, 2024; Richardson et al., 2025). By leveraging the archived human tissue, spatial biology approaches maximize the value of precious clinical specimens while accelerating mechanistic and translational discovery.

Challenges and Future Directions

Despite remarkable progress, challenges remain before spatial proteomics can achieve its full potential in neuroscience research. For example, reproducibility and standardization across platforms, institutions, and analytical pipelines will continue to improve. Antibody validation, batch effects, tissue-processing variability, and segmentation errors can influence downstream interpretation. These issues are particularly important in human postmortem tissue studies where fixation quality, postmortem interval, and pathological heterogeneity introduce additional complexity. In this context, protein-based spatial measurements are often more robust to the tissue-processing variability that affects RNA-based analyses, providing a more stable foundation for cell segmentation, cellular identification, and pathological interpretation while remaining highly complementary to spatial transcriptomics.

Computational analysis also remains challenging. Spatial proteomics datasets are inherently high dimensional and often require integration across modalities, scales, and cohorts. Developing standardized analytical frameworks capable of distinguishing biological signal from technical variation remains an active area of investigation. Future analytical approaches may need to move beyond purely atlas-driven categorization approaches toward methods specifically designed to identify and interrogate abnormal or poorly classified cellular states. Rather than forcing all observed cells into predefined bins, future pipelines could place greater emphasis on understanding how pathological cellular states emerge, interact with neighboring cells, and influence the surrounding microenvironment during disease progression.

Beyond these technical and computational challenges, a more fundamental limitation concerns interpretation: spatial association alone does not establish mechanistic causality. Many current studies remain largely descriptive, identifying pathology-associated molecular states without directly determining whether those states drive degeneration, compensate for injury, or simply reflect downstream consequences of disease. Integrating spatial proteomics with functional experimental systems will therefore be critical for establishing causal relationships.

Future advances will likely focus on improving proteomic depth, increasing three-dimensional scalability, expanding multimodal integration, and enhancing cross-platform reproducibility. Simultaneously, the field must continue transitioning from atlas generation toward hypothesis-driven mechanistic neuroscience capable of resolving dynamic biological processes across time and space.

Conclusion

Spatial proteomics is rapidly reshaping neuroscience by enabling direct investigation of molecular pathways within intact tissue environments. Building on advances in transcriptomics and other histological technologies, these approaches preserve spatial organization while directly measuring protein states, posttranslational modifications, and cellular interactions within their native anatomical context. As multimodal integration strategies mature,

combining proteomics with transcriptomics, glycomics, computational atlasing, neuropathology, and functional studies will provide increasingly comprehensive datasets for interpreting of aging and neurodegeneration across scales ranging from subcellular signaling to large-scale circuit organization. Ultimately, these integrated approaches have the potential to accelerate mechanistic discovery, refine disease classification, identify therapeutic targets, and improve biomarker development.

References

Aebersold R, Mann M (2016) Mass-spectrometric exploration of proteome structure and function. Nature 537:347–355.

Agasti SS, Wang Y, Schueder F, Sukumar A, Jungmann R, Yin P (2017) DNA-barcoded labeling probes for highly multiplexed exchange-PAINT imaging. Chem Sci 8:3080–3091.

Al-Dalahmah O, Sosunov AA, Shaik A, Ofori K, Liu Y, Vonsattel JP, Adorjan I, Menon V, Goldman JE (2020) Single-nucleus RNA-seq identifies Huntington disease astrocyte states. Acta Neuropathol Commun 8:19.

Albertini G, et al. (2026) The Alzheimer's therapeutic Lecanemab attenuates Abeta pathology by inducing an amyloid-clearing program in microglia. Nat Neurosci 29:100–110.

Ali M, et al. (2026) Large-scale CSF and plasma proteomics reveal immune, synaptic, and extracellular matrix disruptions across neurodegenerative diseases. Neuron 114:2549–2565.

Angelo M, et al. (2014) Multiplexed ion beam imaging of human breast tumors. Nat Med 20:436–442.

Angerstein AO, Young LE, Thanasupawat T, Vriend J, Grimsley G, Lun X, Senger DL, Sinha N, Beiko J, Pitz M (2025) Distinct spatial N-glycan profiles reveal glioblastoma-specific signatures. J Pathol 265:486–501.

Arrastia MV, Jachowicz JW, Ollikainen N, Curtis MS, Lai C, Quinodoz SA, Selck DA, Ismagilov RF, Guttman M (2022) Single-cell measurement of higher-order 3D genome organization with scSPRITE. Nat Biotechnol 40:64–73.

Barthelemy NR, et al. (2023) CSF tau phosphorylation occupancies at T217 and T205 represent improved biomarkers of amyloid and tau pathology in Alzheimer's disease. Nat Aging 3:391–401.

Bateman RJ, et al. (2019) Plasma biomarkers of AD emerging as essential tools for drug development: an EU/US CTAD task force report. J Prev Alzheimers Dis 6:169–173.

Bates GP, et al. (2015) Huntington disease. Nat Rev Dis Primers 1:15005.

Bathe T, Hery GP, Villareal JAB, Phillips JL, Cohen EM, Sharma RV, Tsering W, Prokop S (2024) Disease and brain region specific immune response profiles in neurodegenerative diseases with pure and mixed protein pathologies. Acta Neuropathol Commun 12:54.

Belton JM, McCord RP, Gibcus JH, Naumova N, Zhan Y, Dekker J (2012) Hi-C: a comprehensive technique to capture the conformation of genomes. Methods 58:268–276.

Blevins BL, et al. (2021) Brain arteriolosclerosis. Acta Neuropathol 141:1–24.

Boyle PA, Yu L, Leurgans SE, Wilson RS, Brookmeyer R, Schneider JA, Bennett DA (2019) Attributable risk of Alzheimer's dementia attributed to age-related neuropathologies. Ann Neurol 85:114–124.

Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 82:239–259.

Brundin P, Melki R, Kopito R (2010) Prion-like transmission of protein aggregates in neurodegenerative diseases. Nat Rev Mol Cell Biol 11:301–307.

Buccitelli C, Selbach M (2020) mRNAs, proteins and the emerging principles of gene expression control. Nat Rev Genet 21:630–644.

Caughey B, Race RE, Chesebro B (1988) Detection of prion protein mRNA in normal and scrapie-infected tissues and cell lines. J Gen Virol 69:711–716.

Chen WT, et al. (2020) Spatial transcriptomics and in situ sequencing to study Alzheimer's disease. Cell 182:976–991 e919.

Chesebro B, et al. (1985) Identification of scrapie prion protein-specific mRNA in scrapie-infected and uninfected brain. Nature 315:331–333.

Chinta SJ, et al. (2018) Cellular senescence is induced by the environmental neurotoxin paraquat and contributes to neuropathology linked to Parkinson's disease. Cell Rep 22:930–940.

Chung K, et al. (2013) Structural and molecular interrogation of intact biological systems. Nature 497:332–337.

Clarke HA, Ma X, Shedlock CJ, Medina T, Hawkinson TR, Wu L, Ribas RA, Keohane S, Ravi S, Bizon JL (2025) Spatial mapping of the brain metabolome lipidome and glycome. Nat Commun 16:4373.

Coukos R, Krainc D (2024) Key genes and convergent pathogenic mechanisms in Parkinson disease. Nat Rev Neurosci 25:393–413.

de Calignon A, Spires-Jones TL, Pitstick R, Carlson GA, Hyman BT (2009) Tangle-bearing neurons survive despite disruption of membrane integrity in a mouse model of tauopathy. J Neuropathol Exp Neurol 68:757–761.

Dehkordi SK, et al. (2021) Profiling senescent cells in human brains reveals neurons with CDKN2D/p19 and tau neuropathology. Nat Aging 1:1107–1116.

de Laat W, Dekker J (2012) 3C-based technologies to study the shape of the genome. Methods 58:189–191.

De Strooper B, Karran E (2016) The cellular phase of Alzheimer's disease. Cell 164:603–615.

Dickson DW (2009) Neuropathology of non-Alzheimer degenerative disorders. Int J Clin Exp Pathol 3:1–23.

Dileep V, et al. (2023) Neuronal DNA double-strand breaks lead to genome structural variations and 3D genome disruption in neurodegeneration. Cell 186:4404–4421 e4420.

Dong K, et al. (2025) Benchmarking multi-slice integration and downstream applications in spatial transcriptomics data analysis. Genome Biol 26:318.

Drummond E, Nayak S, Pires G, Ueberheide B, Wisniewski T (2018) Isolation of amyloid plaques and neurofibrillary tangles from archived Alzheimer's disease tissue using laser-capture microdissection for downstream proteomics. Methods Mol Biol 1723:319–334.

Drummond ES, Nayak S, Ueberheide B, Wisniewski T (2015) Proteomic analysis of neurons microdissected from formalin-fixed, paraffin-embedded Alzheimer's disease brain tissue. Sci Rep 5:15456.

Dunne J, et al. (2023) Evaluation of antibody-based single cell type imaging techniques coupled to multiplexed imaging of N-glycans and collagen peptides by matrix-assisted laser desorption/ionization mass spectrometry imaging. Anal Bioanal Chem 415:7011–7024.

Duyckaerts C, Delatour B, Potier MC (2009) Classification and basic pathology of Alzheimer disease. Acta Neuropathol 118:5–36.

Foiani MS, et al. (2026) Spatial single-cell proteomics reveals molecular trajectories of tangle-bearing neurons in Alzheimer's disease. *bioRxiv*, 2026.2004.2026.720932.

Fruhwurth S, Zetterberg H, Paludan SR (2024) Microglia and amyloid plaque formation in Alzheimer's disease - evidence, possible mechanisms, and future challenges. J Neuroimmunol 390:578342.

Gabitto MI, et al. (2024) Integrated multimodal cell atlas of Alzheimer's disease. Nat Neurosci 27:2366–2383.

Gao C, Yang C, Zhang L (2025) A graph neural network-based spatial multi-omics data integration method for deciphering spatial domains. PLoS Comput Biol 21:e1013546.

Gate D, et al. (2020) Clonally expanded CD8T cells patrol the cerebrospinal fluid in Alzheimer's disease. Nature 577:399–404.

Gate D, et al. (2021) CD4(+) T cells contribute to neurodegeneration in Lewy body dementia. Science 374:868–874.

Gerdes MJ, et al. (2013) Highly multiplexed single-cell analysis of formalin-fixed, paraffin-embedded cancer tissue. Proc Natl Acad Sci U S A 110: 11982–11987.

Gerrits E, et al. (2022) Neurovascular dysfunction in GRN-associated frontotemporal dementia identified by single-nucleus RNA sequencing of human cerebral cortex. Nat Neurosci 25:1034–1048.

Goltsev Y, Samusik N, Kennedy-Darling J, Bhate S, Hale M, Vazquez G, Black S, Nolan GP (2018) Deep profiling of mouse splenic architecture with CODEX multiplexed imaging. Cell 174:968–981 e915.

Gonzalez-Ortiz F, Kac PR, Brum WS, Zetterberg H, Blennow K, Karikari TK (2023) Plasma phospho-tau in Alzheimer's disease: towards diagnostic and therapeutic trial applications. Mol Neurodegener 18:18.

Grubman A, et al. (2019) A single-cell atlas of entorhinal cortex from individuals with Alzheimer's disease reveals cell-type-specific gene expression regulation. Nat Neurosci 22:2087–2097.

Grundemann J, Schlaudraff F, Liss B (2011) UV-laser microdissection and mRNA expression analysis of individual neurons from postmortem Parkinson's disease brains. Methods Mol Biol 755:363–374.

Guise AJ, et al. (2024) TDP-43-stratified single-cell proteomics of postmortem human spinal motor neurons reveals protein dynamics in amyotrophic lateral sclerosis. Cell Rep 43:113636.

Gut G, Herrmann MD, Pelkmans L (2018) Multiplexed protein maps link subcellular organization to cellular states. Science 361:6401.

Haber E, Deshpande A, Ma J, Krieger S (2025) Unified integration of spatial transcriptomics across platforms. *bioRxiv*.

Habib N, et al. (2020) Disease-associated astrocytes in Alzheimer's disease and aging. Nat Neurosci 23:701–706.

Hawkinson TR, Clarke HA, Young LE, Conroy LR, Markussen KH, Kerch KM, Johnson LA, Nelson PT, Wang C, Allison DB (2022) In situ spatial glycomic imaging of mouse and human Alzheimer's disease brains. Alzheimers Dement 18:1721–1735.

Hawkinson TR, et al. (2026) Hyperglycosylation is a metabolic driver of Alzheimer's disease. Nat Metab 8:1410–1425.

He S, et al. (2022) High-plex imaging of RNA and proteins at subcellular resolution in fixed tissue by spatial molecular imaging. Nat Biotechnol 40: 1794–1806.

Hickey JW, et al. (2022) Spatial mapping of protein composition and tissue organization: a primer for multiplexed antibody-based imaging. Nat Methods 19:284–295.

Hodge RD, et al. (2019) Conserved cell types with divergent features in human versus mouse cortex. Nature 573:61–68.

Hondius DC, et al. (2021) The proteome of granulovacuolar degeneration and neurofibrillary tangles in Alzheimer's disease. Acta Neuropathol 141:341–358.

Hong F, Kishi JY, Delgado RN, Jeong J, Saka SK, Su H, Cepko CL, Yin P (2024) Thermal-plex: fluidic-free, rapid sequential multiplexed imaging with DNA-encoded thermal channels. Nat Methods 21:331–341.

Horie K, et al. (2025) Plasma MTBR-tau243 biomarker identifies tau tangle pathology in Alzheimer's disease. Nat Med 31:2044–2053.

Hosogane T, Casanova R, Bodenmiller B (2023) DNA-barcoded signal amplification for imaging mass cytometry enables sensitive and highly multiplexed tissue imaging. Nat Methods 20:1304–1309.

Hu Y, Lin Z, Xie M, Yuan W, Li Y, Rao M, Liu YH, Shen W, Zhang L, Zhou XM (2025) Maskgraphene: an advanced framework for interpretable joint representation for multi-slice, multi-condition spatial transcriptomics. Genome Biol 26:380.

Hudson HR, Riessland M, Orr ME (2024) Defining and characterizing neuronal senescence, 'neurescence', as G(X) arrested cells. Trends Neurosci 47:971–984.

Hyman BT, et al. (2012) National institute on aging-Alzheimer's association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement 8:1–13.

Irwin KE, et al. (2024) Author correction: a fluid biomarker reveals loss of TDP-43 splicing repression in presymptomatic ALS-FTD. Nat Med 30: 1504.

Jackson HW, et al. (2020) The single-cell pathology landscape of breast cancer. Nature 578:615–620.

Jennings D, et al. (2022) Preclinical and clinical evaluation of the LRRK2 inhibitor DNL201 for Parkinson's disease. Sci Transl Med 14:eabj2658.

Jha D, Blennow K, Zetterberg H, Savas JN, Hanrieder J (2024) Spatial neurolipidomics-MALDI mass spectrometry imaging of lipids in brain pathologies. J Mass Spectrom 59:e5008.

Johnston KG, Berackey BT, Tran KM, Gelber A, Yu Z, MacGregor GR, Mukamel EA, Tan Z, Green KN, Xu X (2025) Single-cell spatial transcriptomics reveals distinct patterns of dysregulation in non-neuronal and neuronal cells induced by the Trem2(R47H) Alzheimer's risk gene mutation. Mol Psychiatry 30:461–477.

Kamath T, Abdulraouf A, Burris SJ, Langlieb J, Gazestani V, Nadaf NM, Balderrama K, Vanderburg C, Macosko EZ (2022) Single-cell genomic profiling of human dopamine neurons identifies a population that selectively degenerates in Parkinson's disease. Nat Neurosci 25:588–595.

Kampmann M (2024) Molecular and cellular mechanisms of selective vulnerability in neurodegenerative diseases. Nat Rev Neurosci 25:351–371.

Kapasi A, DeCarli C, Schneider JA (2017) Impact of multiple pathologies on the threshold for clinically overt dementia. Acta Neuropathol 134:171–186.

Keren-Shaul H, et al. (2017) A unique microglia type associated with restricting development of Alzheimer's disease. Cell 169:1276–1290 e1217.

Keren L, et al. (2018) A structured tumor-immune microenvironment in triple negative breast cancer revealed by multiplexed ion beam imaging. Cell 174:1373–1387 e1319.

Koch A, Tomuro K, Wakigawa T, Morisaki T, Iwasaki S, Stasevich TJ (2026) Bridging single-molecule and genome-wide studies of cellular mRNA translation. RNA 32:520–537.

Kovacs GG, et al. (2016) Aging-related tau astrogliopathy (ARTAG): harmonized evaluation strategy. Acta Neuropathol 131:87–102.

Krasemann S, et al. (2017) The TREM2-APOE pathway drives the transcriptional phenotype of dysfunctional microglia in neurodegenerative diseases. Immunity 47:566–581 e569.

Kronman FN, et al. (2024) Developmental mouse brain common coordinate framework. Nat Commun 15:9072.

Kurnellas M, Mitra A, Schwabe T, Paul R, Arrant AE, Roberson ED, Ward M, Yeh F, Long H, Rosenthal A (2023) Latozinemab, a novel progranulin-elevating therapy for frontotemporal dementia. J Transl Med 21:387.

Larance M, Lamond AI (2015) Multidimensional proteomics for cell biology. Nat Rev Mol Cell Biol 16:269–280.

Leng F, Edison P (2021) Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nat Rev Neurol 17:157–172.

Leng K, et al. (2021) Molecular characterization of selectively vulnerable neurons in Alzheimer's disease. Nat Neurosci 24:276–287.

Leverenz JB, et al. (2007) Proteomic identification of novel proteins in cortical Lewy bodies. Brain Pathol 17:139–145.

Lieberman-Aiden E, et al. (2009) Comprehensive mapping of long-range interactions reveals folding principles of the human genome. Science 326:289–293.

Lin JR, Fallahi-Sichani M, Sorger PK (2015) Highly multiplexed imaging of single cells using a high-throughput cyclic immunofluorescence method. Nat Commun 6:8390.

Ling JP, Pletnikova O, Troncoso JC, Wong PC (2015) TDP-43 repression of nonconserved cryptic exons is compromised in ALS-FTD. Science 349: 650–655.

Ling SC, Polymenidou M, Cleveland DW (2013) Converging mechanisms in ALS and FTD: disrupted RNA and protein homeostasis. Neuron 79:416–438.

Liu Y, Beyer A, Aebersold R (2016) On the dependency of cellular protein levels on mRNA abundance. Cell 165:535–550.

Liu Y, Dai Y, Wang L (2026a) Spatial omics at the forefront: emerging technologies, analytical innovations, and clinical applications. Cancer Cell 44: 24–49.

Liu Y, Zhao S, Yun Z, Xiong F, Peng H (2026b) A mouse brain atlas based on dendritic microenvironments. Nat Neurosci 29:111–122.

Liwang JK, et al. (2025) Epdevatlas: mapping GABAergic cells and microglia in the early postnatal mouse brain. Nat Commun 16:9538.

Long Y, et al. (2024) Deciphering spatial domains from spatial multi-omics with SpatialGlue. Nat Methods 21:1658–1667.

Longo SK, Guo MG, Ji AL, Khavari PA (2021) Integrating single-cell and spatial transcriptomics to elucidate intercellular tissue dynamics. Nat Rev Genet 22:627–644.

Luecken MD, et al. (2022) Benchmarking atlas-level data integration in single-cell genomics. Nat Methods 19:41–50.

Ma M, et al. (2025) The spatial landscape of glial pathology and T cell response in Parkinson's disease substantia nigra. Nat Commun 16:7146.

Maniatis S, et al. (2019) Spatiotemporal dynamics of molecular pathology in amyotrophic lateral sclerosis. Science 364:89–93.

Marx V (2021) Method of the Year 2020: spatially resolved transcriptomics. Nat Methods 18:9–14.

Mathys H, et al. (2019) Single-cell transcriptomic analysis of Alzheimer's disease. Nature 570:332–337.

Meng G, Xu H, Lu D, Li S, Zhao Z, Li H, Zhang W (2023) Three-dimensional chromatin architecture datasets for aging and Alzheimer's disease. Sci Data 10:51.

Merritt CR, et al. (2020) Multiplex digital spatial profiling of proteins and RNA in fixed tissue. Nat Biotechnol 38:586–599.

Miller TM, et al. (2022) Trial of antisense oligonucleotide tofersen for SOD1 ALS. N Engl J Med 387:1099–1110.

Mrdjen D, et al. (2025) Spatial proteomics of Alzheimer's disease-specific human microglial states. Nat Immunol 26:1397–1410.

Munoz-Castaneda R, et al. (2025) A comprehensive atlas of cell type density patterns and their role in brain organization. *bioRxiv*.

Murakami TC, et al. (2018) A three-dimensional single-cell-resolution whole-brain atlas using CUBIC-X expansion microscopy and tissue clearing. Nat Neurosci 21:625–637.

Murray E, et al. (2015) Simple, scalable proteomic imaging for high-dimensional profiling of intact systems. Cell 163:1500–1514.

Musi N, Valentine JM, Sickora KR, Baeuerle E, Thompson CS, Shen Q, Orr ME (2018) Tau protein aggregation is associated with cellular senescence in the brain. Aging Cell 17:e12840.

Nelson PT, et al. (2019) Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. Brain 142:1503–1527.

Network, B. I. C. C. (2021) A multimodal cell census and atlas of the mammalian primary motor cortex. Nature 598:86–102.
Neumann M, et al. (2006) Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 314:130–133.
Nijholt DA, Stingl C, Luider TM (2015) Laser capture microdissection of fluorescently labeled amyloid plaques from Alzheimer's disease brain tissue for mass spectrometric analysis. Methods Mol Biol 1243:165–173.
Ogg J, Postupna N, Gibbons LE, Ariza J, Xiao M, Fonseca LM, Jayadev S, Keene CD, Bird TD, Latimer CS (2025) Down syndrome and a presenilin 2 variant: dual genetic risk of Alzheimer's disease. Acta Neuropathol 150:24.
Otero-Garcia M, et al. (2022) Molecular signatures underlying neurofibrillary tangle susceptibility in Alzheimer's disease. Neuron 110:2929–2948.e2928.
Palmqvist S, et al. (2020) Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. JAMA 324:772–781.
Park J, et al. (2024) Integrated platform for multiscale molecular imaging and phenotyping of the human brain. Science 384:eadh9979.
Pati P, et al. (2022) Hierarchical graph representations in digital pathology. Med Image Anal 75:102264.
Piehl N, et al. (2022) Cerebrospinal fluid immune dysregulation during healthy brain aging and cognitive impairment. Cell 185:5028–5039 e5013.
Piyadasa H, Oberlton B, Ribi M, Leow K, Ranek JS, Averbukh I, Amouzgar M, Liu CC, Franchina DG, Greenwald NF (2026) Multi-omic landscape of human gliomas from diagnosis to treatment and recurrence. Cancer Cell 44:112–128.e116.
Prokop S, Miller KR, Labra SR, Pitkin RM, Hoxha K, Narasimhan S, Changolkar L, Rosenbloom A, Lee VM, Trojanowski JQ (2019) Impact of TREM2 risk variants on brain region-specific immune activation and plaque microenvironment in Alzheimer's disease patient brain samples. Acta Neuropathol 138:613–630.
Quinodoz SA, Bhat P, Chovanec P, Jachowicz JW, Ollikainen N, Detmar E, Soehalim E, Guttman M (2022) SPRITE: a genome-wide method for mapping higher-order 3D interactions in the nucleus using combinatorial split-and-pool barcoding. Nat Protoc 17:36–75.
Radtke AJ, et al. (2020) IBEX: a versatile multiplex optical imaging approach for deep phenotyping and spatial analysis of cells in complex tissues. Proc Natl Acad Sci U S A 117:33455–33465.
Ramakrishnan A, Piehl N, Simonton B, Parikh M, Zhang Z, Teregulova V, van Olst L, Gate D (2024) Epigenetic dysregulation in Alzheimer's disease peripheral immunity. Neuron 112:1235–1248.e1235.
Richardson TE, et al. (2025) Spatial proteomic differences in chronic traumatic encephalopathy, Alzheimer's disease, and primary age-related tauopathy hippocampi. Alzheimers Dement 21:e14487.
Riessland M, et al. (2019) Loss of SATB1 induces p21-dependent cellular senescence in post-mitotic dopaminergic neurons. Cell Stem Cell 25:514–530 e518.
Robinson JL, et al. (2023) Pathological combinations in neurodegenerative disease are heterogeneous and disease-associated. Brain 146:2557–2569.
Rocha EM, De Miranda B, Sanders LH (2018) Alpha-synuclein: pathology, mitochondrial dysfunction and neuroinflammation in Parkinson's disease. Neurobiol Dis 109:249–257.
Ross CA, Tabrizi SJ (2011) Huntington's disease: from molecular pathogenesis to clinical treatment. Lancet Neurol 10:83–98.
Ruf WP, et al. (2026) Multi-modal dissection of cell-type specific TDP-43 pathology in the motor cortex. Nat Commun 17:2406.
Saka SK, et al. (2019) Immuno-SABER enables highly multiplexed and amplified protein imaging in tissues. Nat Biotechnol 37:1080–1090.
Sala Frigerio C, et al. (2019) The Major risk factors for Alzheimer's disease: age, sex, and genes modulate the microglia response to abeta plaques. Cell Rep 27:1293–1306 e1296.
Sanchez-Molina P, et al. (2026) Spatial proteomic analysis in human Alzheimer's disease brains enables identification of microenvironment-dependent microglial cell states. Nat Neurosci 29:1599–1614.
Schaeffer S, Iadecola C (2021) Revisiting the neurovascular unit. Nat Neurosci 24:1198–1209.
Schjoldager KT, Narimatsu Y, Joshi HJ, Clausen H (2020) Global view of human protein glycosylation pathways and functions. Nat Rev Mol Cell Biol 21:729–749.
Siletti K, et al. (2023) Transcriptomic diversity of cell types across the adult human brain. Science 382:eadd7046.
Sims JR, et al. (2023) Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA 330:512–527.
Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M (1997) Alpha-synuclein in Lewy bodies. Nature 388:839–840.
Sun N, et al. (2023) Single-nucleus multiregion transcriptomic analysis of brain vasculature in Alzheimer's disease. Nat Neurosci 26:970–982.
Sun X, Hudson HR, Orr TC, Koutarapu S, Rosenbloom A, Ingalls M, Braubach O, Keene CD, Beechem JM, Orr ME (2025) Spatial multi-omics workflow and analytical guidelines for Alzheimer's neuropathology. *bioRxiv*.
Surmeier DJ, Obeso JA, Halliday GM (2017) Selective neuronal vulnerability in Parkinson disease. Nat Rev Neurosci 18:101–113.
Sweeney MD, et al. (2019) Vascular dysfunction-the disregarded partner of Alzheimer's disease. Alzheimers Dement 15:158–167.
Tabrizi SJ, et al. (2019) Targeting huntingtin expression in patients with Huntington's disease. N Engl J Med 380:2307–2316.
Takei Y, et al. (2021a) Integrated spatial genomics reveals global architecture of single nuclei. Nature 590:344–350.
Takei Y, Zheng S, Yun J, Shah S, Pierson N, White J, Schindler S, Tischbirek CH, Yuan GC, Cai L (2021b) Single-cell nuclear architecture across cell types in the mouse brain. Science 374:586–594.
Tan CW, et al. (2025) The development of a high-plex spatial proteomic methodology for the characterisation of the head and neck tumour microenvironment. NPJ Precis Oncol 9:191.
Thierry M, et al. (2026) Proteomic remodelling of the neurofibrillary tangle from "PART" to advanced Alzheimer's disease. Res Sq rs.3:rs-8703254.
Tian R, et al. (2025) Integrating cross-sample and cross-modal data for spatial transcriptomics and metabolomics with SpatialMETA. Nat Commun 16:8855.
Traxler L, Lucciola R, Herdy JR, Jones JR, Mertens J, Gage FH (2023) Neural cell state shifts and fate loss in ageing and age-related diseases. Nat Rev Neurol 19:434–443.
Tsering W, Hery GP, Phillips JL, Lolo K, Bathe T, Villareal JA, Ruan IY, Prokop S (2023) Transformation of non-neuritic into neuritic plaques during AD progression drives cortical spread of tau pathology via regenerative failure. Acta Neuropathol Commun 11:190.
Tsering W, Prokop S (2024) Neuritic plaques - gateways to understanding Alzheimer's disease. Mol Neurobiol 61:2808–2821.
Ueda HR, Dodt HU, Osten P, Economo MN, Chandrashekar J, Keller PJ (2020a) Whole-brain profiling of cells and circuits in mammals by tissue clearing and light-sheet microscopy. Neuron 106:369–387.
Ueda HR, Erturk A, Chung K, Gradinaru V, Chedotal A, Tomancak P, Keller PJ (2020b) Tissue clearing and its applications in neuroscience. Nat Rev Neurosci 21:61–79.
Vallianatou T, Angerer TB, Kaya I, Nilsson A, Shariatgorji R, Svenningsson P, Andrén PE (2024) Applying spatial metabolomics to investigate age-and drug-induced neurochemical changes. ACS Chem Neurosci 15:2822–2829.
van Olst L, et al. (2025) Microglial mechanisms drive amyloid-beta clearance in immunized patients with Alzheimer's disease. Nat Med 31:1604–1616.
Vicari M, Mirzazadeh R, Nilsson A, Shariatgorji R, Bjärterot P, Larsson L, Lee H, Nilsson M, Foyer J, Ekvall M (2024) Spatial multimodal analysis of transcriptomes and metabolomes in tissues. Nat Biotechnol 42:1046–1050.
Vijayaragavan K, et al. (2022) Single-cell spatial proteomic imaging for human neuropathology. Acta Neuropathol Commun 10:158.
Vogel C, Marcotte EM (2012) Insights into the regulation of protein abundance from proteomic and transcriptomic analyses. Nat Rev Genet 13:227–232.
Walker JM, Kazempour Dehkordi S, Fracassi A, Vanschoiack A, Pavenko A, Taglialatela G, Woltjer R, Richardson TE, Zare H, Orr ME (2022) Differential protein expression in the hippocampi of resilient individuals identified by digital spatial profiling. Acta Neuropathol Commun 10:23.
Walker JM, et al. (2024) Spatial proteomics of hippocampal subfield-specific pathology in Alzheimer's disease and primary age-related tauopathy. Alzheimers Dement 20:783–797.
Wallace EN, West CA, McDowell CT, Lu X, Bruner E, Mehta AS, Aoki-Kinoshita KF, Angel PM, Drake RR (2024) An N-glycome tissue atlas of 15 human normal and cancer tissue types determined by MALDI-imaging mass spectrometry. Sci Rep 14:489.
Wang E, et al. (2025) Multiscale proteomic modeling reveals protein networks driving Alzheimer's disease pathogenesis. Cell 188:6186–6204 e6113.
Wang Y, Mandelkow E (2016) Tau in physiology and pathology. Nat Rev Neurosci 17:5–21.

Yan X, et al. (2026) Mosaic integration of spatial multi-omics with SpaMosaic. Nat Genet 58:1126–1137.
Yao Z, et al. (2021) A taxonomy of transcriptomic cell types across the isocortex and hippocampal formation. Cell 184:3222–3241 e3226.
Yao Z, et al. (2023) A high-resolution transcriptomic and spatial atlas of cell types in the whole mouse brain. Nature 624:317–332.
Yoon JH, et al. (2022) Brain lipidomics: from functional landscape to clinical significance. Sci Adv 8:eadc9317.
Zhang Y, Zhang K, Jin C, Shang L, Wu S, Zhang M, Yuan Y, Liu Y, Wang J (2026a) Integrated IP-MS and optoproteomics reveal dynamic remodeling of protein interaction networks during NLRP3 inflammasome activation. Mol Cell Proteomics 25:101595.
Zhang Z, et al. (2026b) Integrated single-cell and spatial transcriptomic profiling in ALS uncovers peripheral-to-central immune infiltration and reprogramming. Nat Neurosci 29:1735–1748.
Zhao M, et al. (2025) Molecularly defined cellular atlas of the entire mouse brain with isotropic single-cell resolution. Nat Commun 16:10167.
Zhong S, et al. (2020) Decoding the development of the human hippocampus. Nature 577:531–536.
Zhou Y, et al. (2020) Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease. Nat Med 26:131–142.
Zwang TJ, et al. (2024) Neurofibrillary tangle-bearing neurons have reduced risk of cell death in mice with Alzheimer's pathology. Cell Rep 43:114574.