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Progress and Prospects of Single-cell and Spatial Omics in Neurodegenerative Diseases

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Abstract. Neurodegenerative diseases (NDDs) are characterized by pronounced cell-type-specific vulnerabilities and heterogeneity in their pathological microenvironments, which traditional bulk tissue omics approaches cannot resolve in terms of cell lineage, state, and spatial context during disease progression. Single-cell and spatial omics have emerged as powerful technologies providing spatiotemporal expression profiles at single-cell resolution. The growing application of these approaches in NDD research is expected to uncover novel disease-associated cell populations, facilitate hypothesis testing, and identify therapeutic targets. In this review, we first outline the major methodologies of single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics, including representative technical platforms and their main features. We then summarize their applications in major NDDS, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and frontotemporal dementia, with an emphasis on different cell types. Finally, we discuss current challenges such as sample limitations, resolution-throughput trade-offs, and data integration issues, and briefly consider future directions for clinical translation, particularly in biomarker discovery and patient stratification.

Keywords: neurodegenerative disease, single-cell transcriptomics, spatial transcriptomics, cell atlas, biomarker

1. Introduction

Neurodegenerative diseases (NDDs) are characterized by progressive neuronal dysfunction and loss, together with cell-type-specific vulnerability and spatial heterogeneity in pathological microenvironments. Multiple cell types, including neurons, astrocytes, oligodendrocytes, microglia, and vascular-associated cells, respond differently during disease progression. This heterogeneity makes it challenging to fully understand disease mechanisms and develop effective therapeutic strategies. With global population aging, the incidence of major NDDs such as Alzheimer's disease (AD) and Parkinson's disease (PD) continues to increase, placing a growing burden on healthcare systems.

At molecular level, NDD pathology involves complex interactions among genetic factors, cellular states, and regional microenvironments. For example, AD is characterized by amyloid-β (Aβ) plaques and tau neurofibrillary tangles, whose distribution follows region-specific patterns and is influenced by genetic variants such as APOE ε4. In addition, mutations in genes such as HTT,

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C9orf72, SOD1, MAPT, and TARDBP are associated with selective neuronal degeneration in other NDDs. These findings highlight the importance of studying disease mechanisms from both cellular and spatial perspectives.

Recent advances in single-cell and spatial omics have made it possible to profile gene expression at cellular resolution while retaining spatial information. Single-cell and single-nucleus RNA sequencing (scRNA-seq and snRNA-seq) can define cell identities and states, whereas spatial transcriptomics enables the mapping of gene expression within intact tissue architecture [1]. The integration of these approaches provides a useful framework for investigating disease mechanisms and constructing high-resolution molecular atlases of NDDs.

2. Overview of single-cell and spatial omics technologies

2.1. Single-cell transcriptomics

Single-cell RNA sequencing (scRNA-seq) technologies can be classified according to their capture and library construction strategies. These include key steps such as cell isolation, microfluidic encapsulation, barcoding, reverse transcription, and sequencing. Plate-based methods (e.g., Smart-seq2) provide full-length transcript coverage with high sensitivity, whereas droplet- and microwell-based platforms (e.g., 10x Genomics Chromium) enable high-throughput profiling of thousands of cells using barcoded oligonucleotides and unique molecular identifiers (UMIs) [2]. Combinatorial indexing approaches further improve scalability, although they introduce additional computational complexity. In practice, we should balance sensitivity, throughput as well as cost when selecting platforms, and droplet-based methods can usually capture 10^3–10^4 cells in one experiment [3].

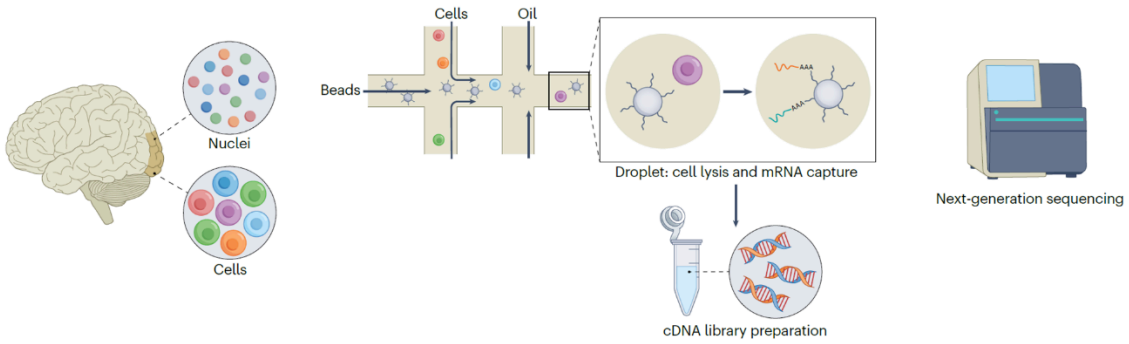

Figure 1. Schematic overview of the droplet-based single-cell RNA sequencing workflow, including cell encapsulation, barcoding, and library preparation

In neuroscience research, single-nucleus RNA sequencing (*snRNA-seq*) can be quite useful because adult brain cells are difficult to dissociate intact. *snRNA-seq* helps profile transcripts from frozen or archived tissues and in principle it can avoid dissociation-induced artifacts [4]. Although nuclear data has unspliced transcripts, cell-type–specific expression signatures can still be preserved and the nuclear data have generally been used to construct human brain cell atlases and characterize disease-associated cellular heterogeneity.

In downstream analysis, single-cell data follows some standard workflows that typically includes quality control, normalization, and clustering moreover. At the same time more attention should be paid to technical artifacts because doublets and ambient RNA contamination can cause problems. Also batch effects should be considered. These analyses can generate gene-cell matrices supporting

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cell-type annotation. Trajectory inference and differential expression analysis across conditions can be done as well.

2.2. Spatial transcriptomics

Spatial transcriptomics can quantify the gene expression when keeping the spatial context of transcripts in intact tissue sections. This is commonly achieved through spatial barcoding or imaging-based approaches that map transcripts onto tissue architecture (Figure 2). This field develops fast and is selected as the Nature Methods' Method of the Year 2020 [5], and this has led to diverse technological strategies that can balance resolution, coverage, as well as throughput.

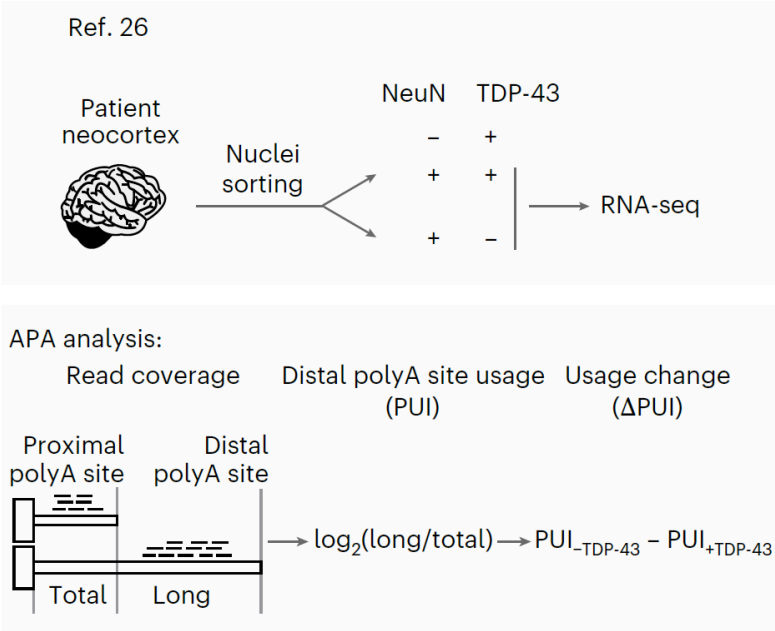

Figure 2. Principle of sequencing-based spatial transcriptomics showing spatial barcoding and mapping of gene expression onto tissue sections

We can divide current methods into three groups broadly. Sequencing-based spatial arrays (e.g., ST, Visium, Slide-seqV2, Stereo-seq) use spacial barcodes capturing transcriptomes through tissue sections to provide genome-wide coverage but typically operate at multi-cellular resolution. They can cover the whole genome, but the resolution is often multi-cellular [6-8]. Imaging-based approaches include multiplexed fluorescence *in situ* hybridization (e.g., MERFISH, seqFISH+) and *in situ* sequencing, can achieve subcellular resolution and single-molecule sensitivity, but these methods are limited to predefined gene panels. Region-of-interest (ROI) profiling platforms, such as GeoMx Digital Spatial Profiler, can enable targeted high-plex analysis of selected tissue regions and are compatible with the formalin-fixed paraffin-embedded (FFPE) samples, helping to integrate with pathological features [9, 10].

Spatial data analysis extends conventional RNA-seq workflows. Image registration and spot-level normalization are applied to incorporate spatial coordinates into data, so that spatial information can be kept in analysis pipeline and used furthermore. Then downstream analyses aim to identify spatial domains and spatially variable genes. This thereby reveals tissue organization and localized molecular programs in the sample, and integration with single-cell data can improve resolution. We can reconstruct cellular composition and interactions within tissue microenvironments, and this

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approach should enable better understanding of cell-cell communication and spatial relationships in complex biological systems cannot be observed using traditional bulk sequencing methods.

2.3. Integration of single-cell and spatial data

Combining single-cell and spatial omics is a focal challenge so far. One common goal is to map the identities of single-cell clusters to tissue coordinates from spatial assays. Deconvolution is one strategy, in which we use single-cell expression signatures as references, and can infer mixture of cell types in every spatial spot or ROI. Tools like RCTD and SPOTlight implement this strategy with reference profiles. Menwhile label transfer or joint embedding is another approach: methods like Seurat's transfer anchors or LIGER align the single-cell profiles with spatial data in a shared low-dimensional space, so that annotate spatial spots by the nearest single-cell cluster. These combined analyses should reveal where each cell type or state is located in tissue [11].

Care must be taken when we evaluate integration results — several limitations should be considered. In spatial data, each spot contains multiple cells, so deconvolution is an inverse problem and may be ambiguous when cell types have similar profiles. Imaging-based spatial platforms only measure a subset of genes, which is complicated to match with scRNA-seq data that covers the whole transcriptome. Batch effects and modality differences (e.g., nuclei vs. whole-cell RNA) may confound direct comparisons. In practice, researchers would validate the integration by checking marker genes, doing spatial permutation tests, or comparing across replicates or control samples. It ultimately aims to put cell-type information with high-resolution back to the tissue map, thus to uncover cellular neighborhoods and cell-cell interactions in situ [12].

3. Applications in neurodegenerative diseases

3.1. Alzheimer's Disease (AD)

The use of single-cell and spatial omics in AD has changed over time. Started from asking "which cell types?", now it has been moved to "which states and where?". Early single-cell studies often focused on which cell types can have expression changes in AD. Some early snRNA-seq studies on human prefrontal and temporal cortex found dozens of neuron and glia subtypes, and specific excitatory neuron subtypes (e.g., those expressing RORB) exhibit marked downregulation of synaptic genes in AD when certain inhibitory interneurons are spared relatively. These studies also found that reactive astrocytes (GFAP-high) and activated microglia are increased in AD samples compared to controls. Particularly, genes like *TREM2* and *CD33*, known AD risk factors, were expressed in microglia mainly, which links genetic risk to that cell type.

Then how these changes connect to disease progression was examined. By profiling AD brains at different Braak stages, researchers can observe continuous trajectories changing in cell states. For instance, neurons in early AD (mild cognitive impairment) can exhibit partial transcriptional shifts, which become more clear in the full-blown dementia. Immune cells show graded activation: microglia upregulate pro-inflammatory genes with plaque burden progressively. A key insight, was there is no single "AD signature" across all the cells. Instead, each cell type transitions along the gradient of states when pathology accumulates.

Spatial transcriptomics can extend AD studies to tissue context. We have found several studies examining "plaque–glia" niche specifically. For instance, when researchers profile cortex regions with Aβ plaques, it reveals that the nearby astrocytes and microglia, and also inhibitory neurons, share coordinated upregulation of immune and phagocytic genes. A spatial experiment in AD

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hippocampus showed that an axis of inflammatory gene expression can radiate outward from dense-core plaques. Genetic context is important: brains of *APOE* ε4 carriers show heightened glial activation around plaques compared to non-carriers, even at similar plaque densities. In sum, spatial data have delineated how gene expression patterns cluster around hallmark lesions of AD [13].

It is vital that these single-cell and spatial insights come together in multi-modal atlases. For example, Seattle AD (SEA-AD) consortium used combined snRNA-seq, snATAC-seq, and Slide-seqV2 on many AD and control brains. This yielded a spatially annotated gene expression atlas of the human temporal cortex. It links cell-type–specific expression modules to local pathology scores. Such atlases can function as reference frameworks and one can query which genes in a given neuronal subtype correlate with tau pathology across cortical layers. Early findings from these resources stress the "atlas-mechanism-biormarker" cycle: single-cell data identify candidate pathways, spatial data map them to lesions, and multi-omic atlases can validate their relevance to patient phenotypes.

3.2. Parkinson's Disease (PD)

PD is characterized by selective loss of midbrain dopaminergic (DA) neurons and accumulation of α-synuclein aggregates called Lewy bodies. Single-cell and spatial omics shed light on understanding PD cell-type specificity. Human single-nucleus studies of substantia nigra have begun to map its cellular composition. DA neurons constitute only a small fraction of SN cells and interpret that heterogeneity exists even among DA neurons (e.g., differing expression of markers like ALDH1A1). Integration with PD genetic data showed that many risk genes (e.g., LRRK2, SNCA, GBA) are expressed in DA neurons and certain glial subtypes, suggesting those as primary disease targets.

In PD research, one technical challenge is that the DA neurons are few and fragile in autopsy tissue, so we can hardly get enough cells for analysis. Many single-cell atlases capture few DA neurons unless specific enrichment is used. To solve this, researchers use fluorescence sorting of neuromelanin-positive nuclei or targeted microdissection of SN. These methods help us do finer analysis: it appears that the most vulnerable DA neuron subclusters (e.g., ventral tier SNpc neurons) have distinct spatial localization patterns along the dorsal–ventral axis of the substantia nigra, and in principle this spatial distribution can explain their selective vulnerability to degeneration (Figure 3).

In spatial aspect, PD research examined both cortex and brainstem environments. In fact, in early cortical PD stages, Lewy pathology can be found in specific layers in neocortex. We can use spatial transcriptomics to profile these layers to identify associated cell-type changes and preliminary results show that affected cortical regions have signatures of immune activation, which hints that interactions between neuronal pathology and peripheral immune cells can exist [14].

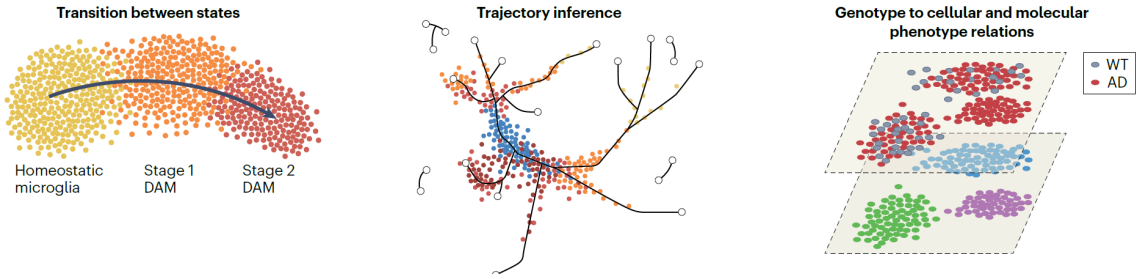

Figure 3. Spatial mapping of dopaminergic neuron subtypes reveals a ventrally localized vulnerable population in Parkinson's disease

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3.3. Other neurodegenerative diseases

The single-cell/spatial toolkit has also been applied to other NDDs. Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD), which often involve TDP-43 proteinopathy, have been studied by single-nucleus RNA-seq of cortex and motor system. These studies found widespread transcriptional dysregulation, particularly of RNA splicing and stress-response pathways, even in cell types not classically implicated by histology [15], and recent evidence further indicates that TDP-43 nuclear loss can drive widespread alternative polyadenylation changes in disease-relevant genes (Figure 4). For example, certain oligodendrocyte subsets in ALS frontal cortex show abnormal expression of heat-shock protein genes, suggesting a global cell stress response. Spatially, investigators are beginning to use organotypic culture slices and human spinal cord sections to map ALS pathology; an emerging question is how motor neuron degeneration signals to surrounding glia in the spinal anterior horn. Some preliminary spatial data indicate that areas of motor neuron loss are accompanied by local oligodendrocyte proliferation signals, pointing to potential cell–cell feedback mechanisms.

Huntington's disease (HD), driven by an expanded *HTT* allele, primarily affects the striatum. Single-cell studies of HD mouse models and patient tissues have documented that medium spiny neurons (MSNs) show dysregulation of genes involved in synaptic connectivity and ion channels. Spatial methods have been used in HD model brains to show that striatal gene expression alterations form gradients, with ventral putamen being most affected. In human HD brain, spatial transcriptomics is still emerging, but one could, for example, use targeted in situ hybridization to detect expanded *HTT* RNA in situ and correlate it with local inflammatory responses.

Rare proteinopathies (such as prion diseases or familial forms of ALS/FTD linked to *FUS*, *SOD1*, or prion protein) have also seen initial single-cell investigations. These often reveal convergent pathways: for instance, early transcriptomic changes in prion-infected brain resemble those in other dementias, including upregulation of innate immunity and synaptic loss genes. Spatial approaches here could eventually map the spread of prion aggregates and identify which cell types first respond. Across these diseases, a recurring theme is that misfolded protein pathology and genetic lesions each imprint distinct but overlapping patterns of cell-type vulnerability, which single-cell/spatial data can begin to disentangle.

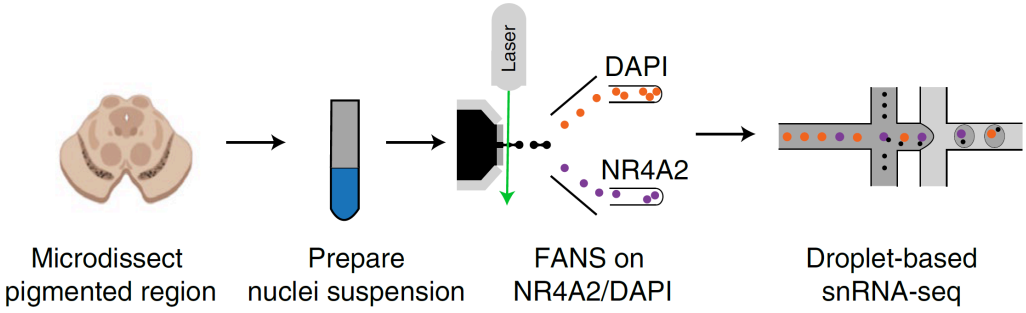

Figure 4. TDP-43 nuclear loss induces widespread alternative polyadenylation changes in disease-relevant genes in FTD/ALS

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4. Current challenges and future directions

4.1. Technical challenges

A major bottleneck in applying single-cell methods to NDD is tissue availability and quality control. Human brain samples inevitably come from postmortem donors, often after delays that degrade RNA. Postmortem interval (PMI) and fixation method (fresh frozen vs. fixed) strongly influence the quality of recovered transcripts. Typically, long PMIs degrade RNA and may lead to dropout of specific transcripts, especially those in long or labile mRNAs. Researchers mitigate this by rapid autopsy protocols and by using snRNA-seq, which recovers more stable nuclear transcripts. However, snRNA-seq has its own biases: it tends to capture unspliced transcripts and may miss abundant cytosolic RNAs. Also, the yield of nuclei can vary by cell type (e.g., large neurons may yield fewer intact nuclei). Protocols continue to evolve to maximize yield and uniformity; for example, recent improvements in nuclei isolation can recover viable nuclei from frozen cortex reliably.

In spatial omics, the resolution–throughput–cost trade-off is stark. Sequencing-based arrays capture all genes but blur multi-cell spots; in situ imaging resolves single molecules but is limited in throughput and gene count. New methods are blending these axes: for example, Seq-scope uses patterned arrays to reach subcellular resolution with near-transcriptome coverage. Users must decide priorities: a wide field-of-view whole-transcriptome map, or a focused high-resolution panel. Any spatial experiment also requires careful tissue handling: protocols often include steps for tissue permeabilization and mRNA capture, which must preserve RNA and morphology. Compatibility with FFPE (standard pathology samples) is also a concern; some spatial kits (like GeoMx DSP) explicitly support FFPE, while others require fresh-frozen tissue [16].

Integration of pathological stains with spatial data poses another challenge. In NDDs, classical neuropathology uses immunohistochemical stains (Aβ, phospho-tau, α-synuclein, TDP-43, etc.) to define lesions. Ideally, one would perform spatial transcriptomics on the same section used for IHC, but simultaneous staining and RNA capture can conflict (some stains degrade RNA). A common compromise is adjacent sections: one stained to locate plaques/tangles, the other used for gene capture, with computational image registration aligning them. Even small misalignments can lead to erroneous interpretation (e.g., misattributing gene signals to a plaque that is actually a few tens of microns away). High-precision image registration algorithms are thus important. Some protocols embed fiducial markers in the tissue to improve alignment. In summary, co-registration of multi-modal pathology data is an active area of methodological development.

4.2. Data integration issues

A central computational challenge is avoiding spurious technical variation. Single-cell datasets often suffer batch effects: donor-to-donor variability, library preparation differences, and sequencing depth can create artifacts. Best practices employ normalization and batch-correction methods that respect count distributions (e.g., modeling RNA-seq count statistics). After integration, one must check that true biological differences are preserved: for example, cell types that should be distinct (e.g., neurons vs. glia) must not be inadvertently merged. Over-correction can be detected if known marker genes lose differential expression. Spatial datasets have analogous issues: spots from different batches or platforms may have different capture efficiencies.

When combining single-cell and spatial data, additional uncertainties arise. A spatial spot (e.g., Visium spot) typically contains multiple cell types, so its expression profile is a mixture.

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Deconvolution algorithms (e.g., nonnegative matrix factorization and probabilistic labeling) can be used to handle this problem, but it is worth noting that the results may be affected by noise. Marker genes may drop out (fail to detect a gene in one modality), and could lead to mismatches. Meanwhile imaging-based methods may include only a subset of genes (< 1000), making it hard to align them to full transcriptomes. A practical approach is modular: one may first identify spatial domains by gene expression clustering, then assign likely cell-type labels to those domains using single-cell reference and ultimately examine domain-specific patterns. Validation is key. Using independent marker stainings or alternative deconvolution methods can help confirm findings. Recent benchmarking studies suggest that if we integrate multiple analytical strategies (e.g., combining deconvolution with label-transfer), we can improve robustness. The initial goal is to ensure "identifiability": the integrated model can reconstruct observed data from plausible cell-type contributions uniquely.

Metadata and ontology can bring more difficulties. Neuroanatomy is complex with many overlapping names (e.g., Brodmann areas vs. hippocampal subfields). Region labels are not consistent across studies (such as "hippocampus CA1" vs. "cornu ammonis 1") and that can make data merging hard. Cell type names are also not fixed. For example, the term "disease-associated microglia (DAM)" is used variably in different papers. Community standards (like the Cell Ontology) and reference atlases (such as the BRAIN Initiative Cell Atlas) are crucial if researchers want to make comparisons across studies. Researchers should annotate data carefully with agreed-upon terms such as using standardized spatial ontologies for brain regions. There are ongoing efforts to develop consensus definitions of neuron and glia subtypes. Until these are settled, integration will need careful curation and possibly manual mapping of related terms [16].

4.3. Clinical translation potential

The main goal of single-cell and spatial omics is to help the clinical practice. There is possibility for technologies to be used as discovery tools and also they can work as diagnostic aids. From abiomarker perspective, cell-level atlases can point out possible molecules that reflect the disease status. For example, if a specific gene module in hippocampal interneurons correlates with cognitive decline, that gene set might be detectable in cerebrospinal fluid or blood as a signature. Spatial mapping adds relevance: genes found upregulated in plaque-adjacent glia could become targets for PET imaging agents. In PD, spatially resolved evidence of DA neuron loss in particular midbrain regions could refine imaging diagnostics (e.g., designing radiotracers that bind to markers of neuron health rather than just dopamine levels).

Practically, spatial methods are particularly attractive because they can be applied to routine clinical samples. FFPE brain tissue, collected at biopsy or autopsy, can be profiled spatially (GeoMx and emerging imaging methods support FFPE). Thus, retrospective clinical cohorts could be studied, linking molecular patterns to patient outcomes. However, clinical adoption requires proven reproducibility. Recent multi-center comparisons have shown that without standardized protocols, variability between labs is high. The community is moving toward solutions: for instance, generating reference datasets (like the "Spatial Touchstone") that allow benchmarking of new experiments. Establishing quality control metrics (e.g., RNA quality score, spot-to-spot consistency) and SOPs will be necessary before spatial omics can be used for diagnosis or monitoring [17].

Finally, single-cell/spatial omics produce high-dimensional hypotheses that must be validated. Integration with genetics and epidemiology can prioritize targets. For example, if multiple independent single-cell studies find the same vulnerable cell type expressing gene X near pathology, and if X also harbors a risk variant or encodes a druggable protein, it becomes a top target.

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Functional assays (in cell or animal models) are needed to test causality. Thus, these omics serve as a roadmap: they highlight promising leads (cell types, pathways, biomarkers) which then guide mechanistic experiments and therapeutic development. In this way, single-cell/spatial insights can be translated into interventions, closing the "bench-to-bedside" loop for neurodegenerative diseases.

5. Conclusions and outlook

Single-cell and spatial omics can push NDD research into new stage of precision anatomy. Diseased brain tissue can be dissected into its constituent cells and we can map their molecular states onto histological structures, and this can help researchers understand spatial distribution of molecular changes. In this review we outline progress when applying these tools to AD, PD, ALS/FTLD, Huntington's disease, and other diseases. In the next step we should overcome current challenges and it is worth noting that we need to improve sample quality, integrate multi-modal data, ensure reproducibility, and thus build full pathological atlases for translational impact.

For the future research, we are looking forward to developing standardized multi-modal brain atlases. For example, brain atlas with full annotation may include single-cell RNA, epigenetic marks, spatial proteomics, and imaging features. These data can come from both healthy and diseased states. This atlas can support virtual experiments and one could "look up" the expression of any gene in any cell type at any location, and this can be done in any disease context. Also, artificial intelligence tools may be trained on these datasets, and then predict disease status or treatment response from single-cell profiles.

In summary, as these technologies mature, they can help change field of neurology in principle. We expect that spatially-informed single-cell profiling will become more common in routine clinical work and it can help patient stratification. Personalized therapy should benefit from this method as well. These approaches reveal which cells are affected and how disease progresses at single-cell level, so targeted interventions and biomarkers can be developed by researchers, ultimately improving diagnosis and treatment of neurodegenerative diseases.

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