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Mapping human brain cell type origin and diseases through single-cell transcriptomics

Anjana Soorajkumar [1], Bipin Balan[2], Nasna Nassir[2,3], Hosneara Akter[4], Zaha Shahin[5], Bakhrom K. Berdiev[3,6], Marc Woodbury-Smith[7], Reem Khalil[8], Babacar Cisse[9], Hani T. S. Benamer[3] and Mohammed Uddin [2,3,6 ✉]

The human brain, a pinnacle of biological complexity, comprises a diverse array of cell types that regulate cognition and maintain neural homeostasis. Advances in single-cell transcriptomics have revolutionized neuroscience by enabling high-resolution molecular profiling, revealing unprecedented insights into cellular heterogeneity, lineage dynamics, and disease-associated states. Large-scale brain-mapping initiatives have identified numerous novel cell types, yet their functional roles in health and disease remain poorly understood. This review synthesizes current knowledge of brain cell diversity, from neurogenesis to pathological states, and highlights key gene markers that define cellular identity and function. By integrating insights from single-cell transcriptomics, we explore how cellular diversity shapes brain function and contributes to disease mechanisms, providing a foundation for future research and translational applications.

INTRODUCTION

The human brain, representing the epitome of biological complexity, comprises a diverse array of cell types that orchestrate cognition, behavior, and neural homeostasis. Over the past two million years, the brain has undergone rapid evolutionary changes, marked by significant expansion and specialization, particularly in the prefrontal cortex (PFC). These adaptations underpin advanced cognitive abilities such as language, decision-making, and memory. Despite these advancements, the cellular and molecular mechanisms driving brain function and disease remain incompletely understood.

A key distinction in human brain evolution lies not merely in size but in its neuronal organization and connectivity. Although Neanderthals possessed larger cranial capacities, *Homo sapiens* exhibit a significantly higher neuronal count and more intricate cortical architecture, highlighting the importance of coordinated brain organization in cognitive evolution. The human cerebral cortex, for instance, contains approximately 16.3 billion neurons [1], far surpassing those of chimpanzees (7.4 billion) [2] and mice (13.7 million) [3]. Comparative studies reveal both conserved and species-specific neuronal features, particularly in circuits governing complex behaviors such as language and higher-order cognition [4, 5]. Understanding this cellular diversity—spanning molecular identity, connectivity, and plasticity—is crucial for unravelling brain function in normal and disease states.

Recent breakthroughs in single-cell transcriptomics have revolutionized neuroscience by enabling high-resolution molecular profiling of individual cells [6]. This technology has unveiled unprecedented insights into cellular heterogeneity, lineage dynamics, and disease-associated states. Large-scale brain-mapping initiatives like the NIH's BRAIN Initiative have identified hundreds of novel cell types [7], yet their functional roles in health and disease remain poorly characterized. For instance, the discovery of human-specific basal radial glia (bRG) subtypes has reshaped our understanding of cortical expansion, yet their role in neurodevelopmental disorders like autism spectrum disorder (ASD) remains underexplored.

In this review, we synthesize current knowledge of brain cell diversity, from neurogenesis to pathological states, and highlight key gene markers that define cellular identity and function. By integrating insights from single-cell transcriptomics, we explore how cellular diversity shapes brain function and contributes to disease mechanisms. This work provides a framework for future research and translational advancements, offering new avenues to address the complexities of the human brain in health and disease.

CELLULAR DIVERSITY IN NEURODEVELOPMENT AND DISEASE
Neurogenesis and brain cell plasticity

The human brain's complexity arises from its diverse array of neurons and glial cells, which orchestrate complex behaviors and cognitive functions (Box 1). Neurogenesis, the process of generating new neurons from neural progenitors [8], is crucial for constructing functional neural circuits (Fig. 1). While embryonic and postnatal neurogenesis establish foundational neural networks critical for

¹Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, New York, NY, USA. ²Center for Applied and Translational Genomics (CATG), Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai Health, Dubai, UAE. ³College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai Health, Dubai, UAE. ⁴Genetics and Genomic Medicine Centre (GGMC), NeuroGen Healthcare, Dhaka, Bangladesh. ⁵UCL Cancer Institute, University College London, London, UK. ⁶GenomeArc Inc., Mississauga, Ontario, Canada. ⁷Department of Psychiatry, Queen's University, Kingston, ON, Canada. ⁸American University of Sharjah, Department of Biology, Chemistry and Environmental Sciences, Sharjah, UAE. ⁹Department of Neurosciences, Dubai Health, Dubai, UAE. ✉email: mohammed.uddin@dubaihealth.ae

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Box 1. Cellular composition of the human brain

The human brain is an exceptionally complex organ composed of two major cellular classes: neurons and glial cells (Fig. 1). Neurons are electrically excitable cells responsible for transmitting chemical or electrical signals, while glial cells provide structural, metabolic, and immunological support. Glia significantly outnumbers neurons—by up to tenfold—and are indispensable for guiding neuronal development, protecting neurons from injury, and enhancing the speed of signal transmission. The central nervous system (CNS) contains four principal glial cell types: astrocytes, oligodendrocytes, microglia, and ependymal cells [97]. Astrocytes regulate blood flow, ion homeostasis, neurotransmitter cycling, and maintain the blood-brain barrier. Oligodendrocytes form myelin sheaths that facilitate rapid signal conduction. Microglia serve as the brain's resident immune cells, engaging in synaptic pruning, phagocytosis, and inflammatory regulation. Ependymal cells line the brain's ventricles and contribute to cerebrospinal fluid (CSF) production and filtration. Single-cell transcriptomic studies have uncovered extensive transcriptional heterogeneity among glial populations, including region-specific astrocyte subtypes, dynamic microglial states, and developmentally regulated oligodendrocyte precursors.

Neurons are broadly classified into excitatory and inhibitory types based on neurotransmitter release. Excitatory glutamatergic neurons—comprising 80–90% of cortical neurons—include layer- and projection-defined subtypes such as L2/3 IT, L5 PT, and L6 CT neurons [98]. Inhibitory GABAergic interneurons (~10–20%) are highly diverse, with canonical subclasses including parvalbumin-positive (PV+), somatostatin-positive (SST+), and VIP+ neurons. These interneurons fine-tune circuit activity and maintain excitation-inhibition balance, critical for sensation, movement, and cognition.

Excitatory neurons typically exhibit spiny morphologies with long apical dendrites and consistent electrophysiological profiles, while inhibitory neurons are more compact, often aspiny, and display greater electrophysiological diversity [99]. As shown in Fig. 1, transcriptomic approaches have enabled high-resolution classification of these neuronal and glial subtypes in the human cortex, revealing species- and region-specific cellular diversity.
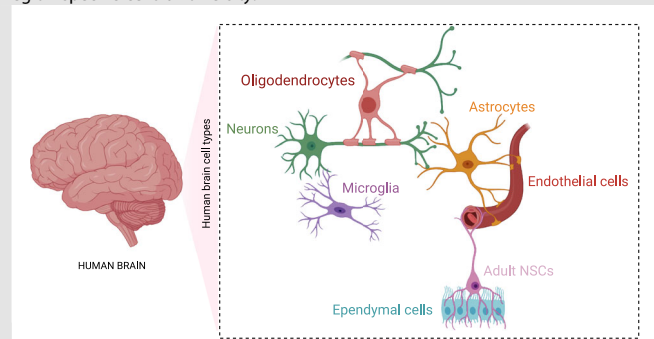
complex behaviors, adult neurogenesis persists in specialized niches like the hippocampal dentate gyrus and olfactory bulbs, integrating new neurons into existing circuits to enhance memory and cognitive plasticity [9]. Recent studies have shown that adult hippocampal neurogenesis is modulated by environmental enrichment and physical exercise, with deficits linked to depression and age-related cognitive decline [10, 11]. This process underscores the brain's remarkable plasticity, enabling adaptation to environmental stimuli and experiences. However, disruptions in neurogenesis have been linked to neurological and psychiatric disorders, such as Alzheimer's disease and depression, highlighting its dual role in health and pathology.

Neocortical evolution

The evolution of the human neocortex, responsible for higher cognitive functions, has seen significant changes in neural stem and progenitor cell (NSPC) populations. Comparative studies across mammals reveal a notable increase in basal progenitors and basal radial glia (bRG) in humans compared to species like mice, which lack these cell types [12–15]. These bRG subtypes, characterized by bifurcated basal processes, are absent in non-human primates (NHPs) such as macaques, suggesting evolutionary adaptations that drive cortical complexity. For example, Florio et al. [16] showed that human bRG cells exhibit prolonged proliferative capacity compared to mouse counterparts, enabling the generation of additional cortical layers [16]. Beyond

progenitors, human-specific microglia in the dorsolateral prefrontal cortex (dlPFC) specialize in synaptic pruning and maintenance, diverging from the immune-focused roles seen in NHPs [17]. Additionally, astrocytes and oligodendrocyte progenitor cells show pronounced human-specific gene expression, enabling enhanced intercellular communication critical for higher cognition. Human astrocytes express distinct calcium signaling pathways that enhance their ability to modulate neuronal activity, a feature absent in chimpanzees [18].

These evolutionary innovations not only enhance cognitive abilities but also reveal vulnerabilities. Changes in human-specific neural stem cell populations, such as basal radial glia (bRG) and intermediate progenitors, have contributed to the complexity of the human cortex. However, disruptions in these cell types are associated with neurological disorders, including epilepsy, intellectual disability, and cortical malformations, highlighting the delicate balance between evolutionary advantages and developmental risks [19]. Additionally, enhanced astrocyte-microglia interactions, while crucial for brain function, may exacerbate neuroinflammatory responses in aging and Alzheimer's disease [20, 21]. Importantly, emerging evidence indicates that human astrocytes and microglia display distinct molecular, morphological, and functional features compared to other species, suggesting that these interactions may have unique characteristics in the human brain that influence disease susceptibility [22, 23]. The interplay between evolutionary adaptations and disease susceptibility underscores the importance of studying human-specific cell types in both health and pathology. These examples illustrate how evolutionary trade-offs predispose the human brain to neurodevelopmental and neurodegenerative disorders. To understand the mechanisms underlying these pathologies, researchers are increasingly leveraging cutting-edge technologies, such as single-cell transcriptomics and multi-omics integration, to resolve cellular heterogeneity with unprecedented precision. In the following section, we explore how these breakthroughs are decoding the molecular architecture of brain cells and bridging evolutionary insights with clinical translation.

CELLULAR DYNAMICS USING SINGLE-CELL TECHNOLOGIES
Single-cell RNA sequencing and spatial transcriptomics

Brain transcriptome atlases, such as the Allen Human Brain Atlas, BrainSpan Atlas, and datasets from PsychENCODE have become invaluable tools for deciphering gene expression patterns across different brain regions and developmental stages in mammals [24–26]. Early studies revealed variations in messenger ribonucleic acid (mRNA) transcript abundance between human and NHP brains, providing crucial insights into the evolution of the primate brain transcriptome [27–29]. Furthermore, alternative splicing (AS) enhances transcriptome complexity, with the adult human brain exhibiting a higher AS prevalence, contributing significantly to evolutionary diversity [30, 31]. While traditional bulk RNA sequencing (RNA-seq) has identified differentially expressed genes (DEGs) in various diseases, its limitation lies in capturing cellular nuances and potential false positives due to sample variability.

Recent breakthroughs in next-generation sequencing (NGS), single-cell isolation techniques, and molecular barcoding have revolutionized the generation of cDNA libraries from individual cells. The initial single-cell transcriptome analysis using NGS focused on early developmental stages, with subsequent innovations such as droplet-based microfluidic methods—including Drop-seq and inDrop—greatly enhancing the scalability and efficiency of single-cell RNA sequencing (scRNA-seq) [32]. Figure 2a outlines a representative scRNA-seq workflow, from sample preparation and RNA capture to primary, secondary, and tertiary computational analyses. While this workflow is commonly
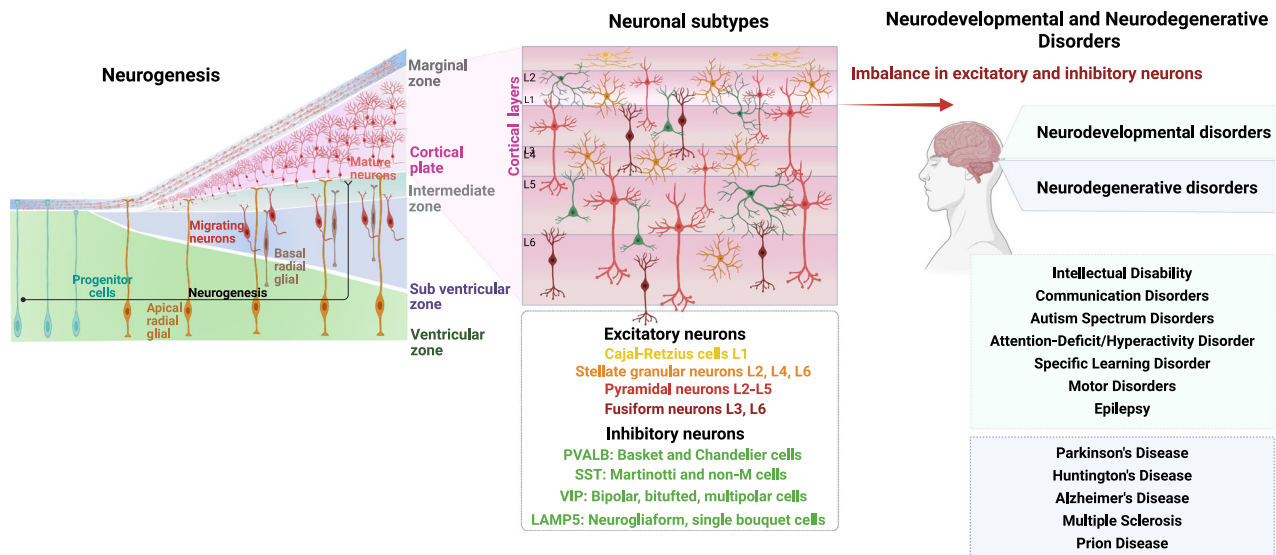
Fig. 1 Neurogenesis during fetal brain development, cortical neuronal subtypes, and associated neurodevelopmental and neurodegenerative disorders. The left panel shows fetal neurogenesis in the developing neocortex, highlighting progenitor zones (ventricular, subventricular, intermediate) and migrating neurons. The middle panel depicts mature cortical layers with excitatory and inhibitory neurons. The right panel presents neurodevelopmental and neurodegenerative disorders linked to neuronal imbalances. Figure created using BioRender.com.

illustrated, we include it here to contextualize the analytical layers discussed later in this review. These high-throughput techniques enable the simultaneous capture and barcoding of thousands of single cells, significantly improving resolution and throughput. Extensive reviews have detailed the experimental workflow (Fig. 2a) of these technologies [33]. Moreover, the integration of single-cell technologies with rapid advancements in computational tools has ushered in a transformative era in this field. Supplementary Table 1 provides a compilation of various scRNA-seq techniques and commonly used bioinformatics tools for analysis.

Obtaining fresh human brain tissue for single-cell gene expression studies poses significant challenges. Single-nucleus RNA sequencing (snRNA-seq) has emerged as a viable solution, analyzing frozen post-mortem samples to characterize cellular diversity and isolate nuclei, particularly from complex cell types such as neurons [34]. Widely adopted in brain research, snRNA-seq enables the analysis of archived clinical materials in brain banks. While nuclei datasets may lack certain transcripts, snRNA-seq consistently replicates single-cell studies. Despite challenges, rapid advancements in scRNA-seq protocols and bioinformatics tools are expanding capabilities, enabling researchers to address questions beyond the scope of bulk transcriptomics.

Recent advancements in scRNA-seq have profoundly enhanced our understanding of the human brain and beyond. This technique has identified novel cell types and subtypes [35], characterized rare cell populations [36], and provided insights into evolutionary dynamics [37]. It has influenced established differentiation hierarchies, revealing insights into random allelic gene expression, developmental changes, and responses to stimuli [38]. Moreover, scRNA-seq distinguishes between normal and abnormal cells and identifies cell types linked to various pathological conditions [39]. Figure 2b illustrates its wide-ranging applications, including its role in uncovering disease-specific molecular mechanisms, potentially leading to new drug targets and biomarkers. Despite its maturity, the transformative impact of scRNA-seq lies in its ability to manage vast datasets, positioning it as a cornerstone of single-cell resolution technology in biomedical research and a potent source of untapped knowledge.

The influx of scRNA-seq data has led to a paradigm shift in classifying brain cell types. Initiatives like the Human Cell Atlas have realized the goal of comprehensively characterizing every human cell. Although, not yet widely applied in the studies summarized in this review, emerging integrative methods, such as combining biocytin staining (for neuronal morphology) [40], patch-seq (linking transcriptomics with electrophysiology) [41], and multiplexed error-robust fluorescence in situ hybridization MERFISH (spatial transcriptomics) [42], are enhancing the interpretability of single-cell data by connecting molecular signatures with cellular function and spatial context. These methods represent future directions that may further refine brain cell type classification and disease understanding. Furthermore, integrating single-projection neuron morphology with transcriptomic profiles confirms that molecular signatures align with major neuronal projection types, refining our understanding of brain circuits and functional organization.

Multi-omics integration

Building on these advances, cross-modal investigations are essential for achieving comprehensive single-cell anatomical mapping and refining cell type classifications in both healthy and pathological brain tissues. The potential of scRNA-seq extends beyond classification to investigating cellular responses to genetic perturbations through techniques like perturb-seq [43], which systematically introduces genetic modifications and captures their transcriptomic consequences at single-cell resolution. To gain deeper insights into cellular states, researchers are increasingly adopting single-cell multi-omics, which integrates transcriptomic data with proteomic, metabolomic, or chromatin accessibility information. For instance, cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq) combines scRNA-seq with protein-marker detection using oligonucleotide-conjugated antibodies, allowing simultaneous analysis of gene expression and surface protein levels [44]. These multi-omics approaches hold immense potential for unraveling the molecular networks governing individual brain cells, enabling deeper investigations into neurodevelopment, pathology, and evolution.

While these insights have significantly advanced our understanding of human cellular dynamics, a fundamental question arises: how do these processes compare across species? To address this, recent studies have leveraged single-cell technologies for systematic cross-species comparisons, revealing both conserved and human-specific features of brain organization.
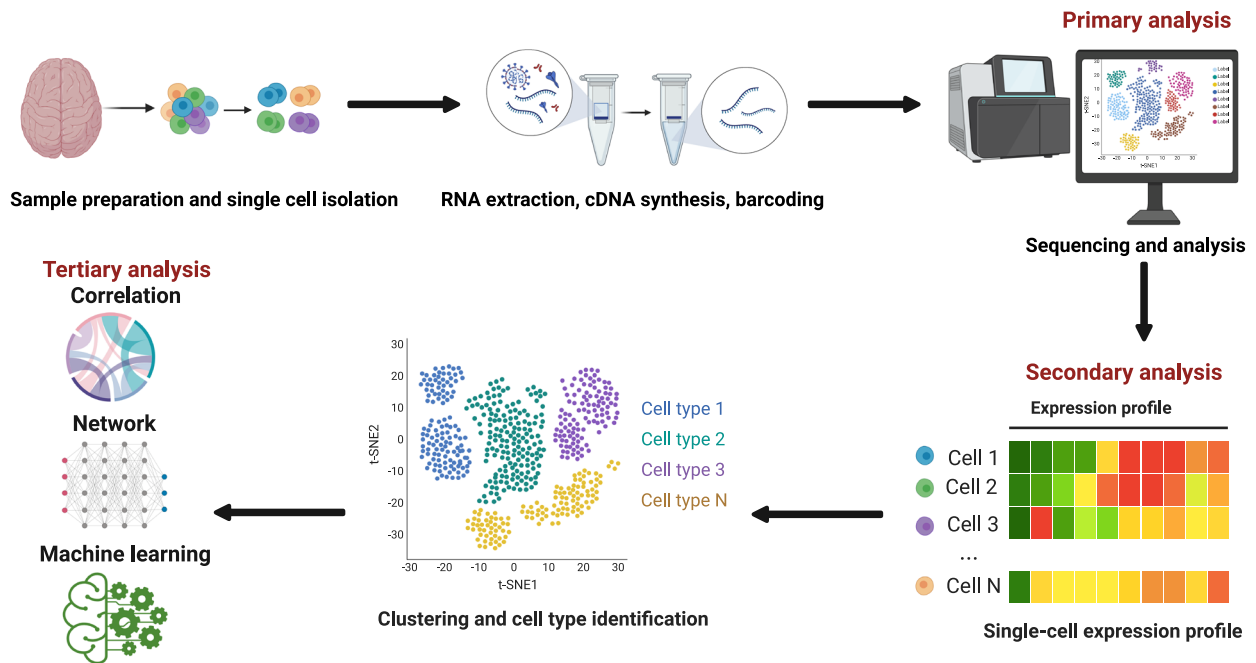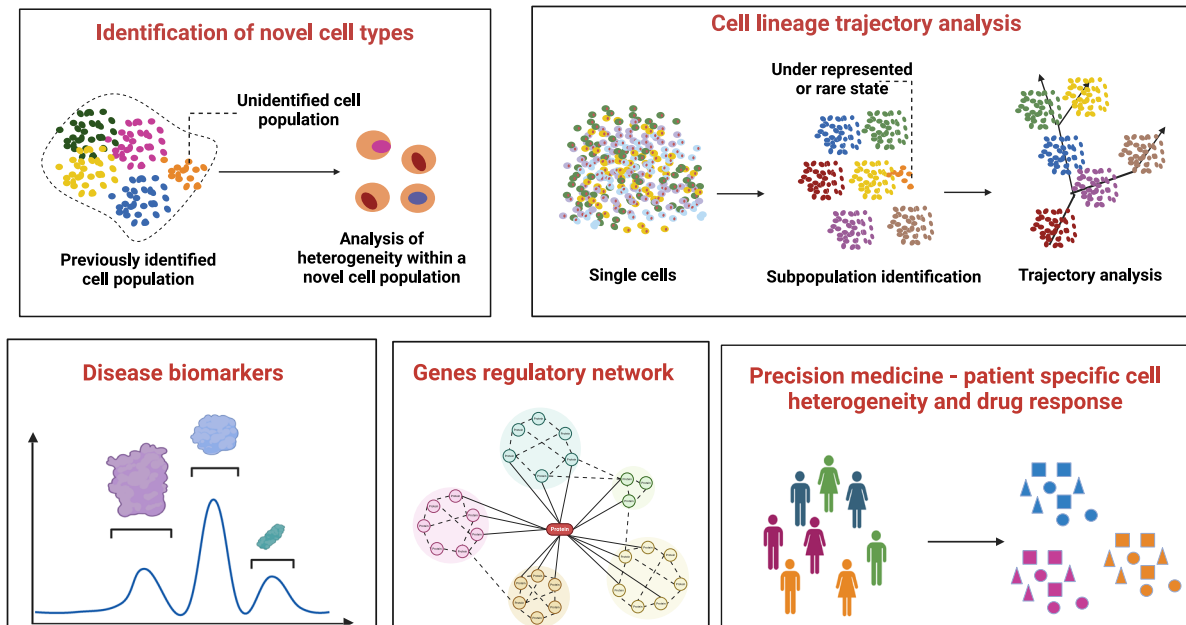
Fig. 2 Single-cell RNA sequencing technology. a Workflow of scRNA-seq experiment. Schematic representation outlining the sequential steps involved in scRNA-seq, including single-cell isolation, cDNA synthesis, library preparation, sequencing, and subsequent data analysis. **b** Applications of scRNA-seq. Illustration highlighting diverse applications of scRNA-seq, ranging from cell type identification to dissecting cellular heterogeneity in complex biological systems. Figure created with BioRender.com.

NOVEL CELL TYPES REVEALED BY SINGLE-CELL TRANSCRIPTOMICS

In addition to the well-characterized bRG, recent scRNA-seq and snRNA-seq studies have identified previously unrecognized or novel brain cell populations. Among these, rosehip neurons represent a distinct subtype of layer 1 GABAergic interneurons,

characterized by dense axonal arborization and restricted expression of canonical interneuron markers [45]. These cells have been identified exclusively in the human cortex and are hypothesized to modulate local microcircuit activity through targeted inhibitory signaling. Human-specific astrocyte subtypes have also been defined, marked by elevated expression of

calcium signaling genes and transcriptional programs implicated in synaptic support and modulation, suggesting expanded functional roles relative to rodent astrocytes [27]. In neurodegenerative conditions, reactive hybrid glial populations—co-expressing astrocytic and oligodendrocyte precursor cell (OPC) markers—have been detected in both epilepsy and Alzheimer's disease, implicating them in neuroinflammatory processes and gliosis [46]. Furthermore, scRNA-seq analyses have delineated distinct microglial subpopulations with developmentally restricted neuroprotective or pro-inflammatory transcriptional signatures, highlighting their dynamic and context-dependent roles in immune surveillance and neural remodeling [47]. During mid-gestational cortical development, transitional excitatory neuronal populations with unique and time-specific gene expression profiles have also been identified, underscoring critical windows of circuit formation [48]. Collectively, these findings exemplify the utility of single-cell transcriptomic technologies in refining brain cell taxonomies and uncovering novel cellular phenotypes and states relevant to both normal brain function and pathology.

Cross-species atlases

Recent advancements in single-cell technologies have revolutionized our ability to assess gene expression in thousands of individual cells simultaneously, facilitating detailed cross-species comparisons. This has enabled researchers to discern how differences in the diversity and abundance of cell types, rather than merely transcriptional variations, might underlie species-specific brain functions. Integrated transcriptomic and epigenomic analyses within the primary motor cortex (M1) of humans, NHPs, and mice have exemplified this progress, leading to the creation of comprehensive reference datasets like the Azimuth reference dataset [49–51]. This dataset consolidates maps from various single-cell references, including those relevant to brain data. Figure 3 represents the taxonomy of different cells derived from the primary motor cortex (M1) of human, marmoset, and mice. This comprehensive analysis, involving over 450,000 nuclei, has unveiled a multimodal, hierarchical classification of approximately 100 unique cell types in each species (Supplementary Table 2). These cell types exhibit distinct marker gene expression patterns and specific sites of accessible chromatin.

To delve deeper into human brain cellular composition and complexity, the National Institutes of Health's (NIH) Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative—Cell Census Network (BICCN)—has united diverse laboratories from multiple disciplines. Their collective mission is to systematically identify, characterize, and map every cell type within the brains of humans, NHPs, and rodents, encompassing molecular, electrophysiological, and morphological attributes. Siletti initiated the foundational work for the atlas by meticulously sequencing the RNA of over 3 million individual cells drawn from 106 distinct regions spanning the entirety of the human brain [52]. This analysis characterized 461 overarching classifications of brain cell types (Supplementary Table 3), encompassing an impressive array of over 3000 distinct subtypes.

Human-specific regulation

Despite significant efforts in characterizing brain cell types, we have yet to determine the role of human-specific genes and the specific brain cells they regulate. A comparative analysis of humans and our closest evolutionary relatives, chimpanzees and gorillas, reveals shared brain cell types with notable differences in the genes that regulate them [53]. These variations include genes associated with neuronal connections and neural circuit formation, suggesting that the enhancement of cognitive abilities during evolution may result from the adaptation of similar cell types in brain circuitry or the fine-tuning of their functions. Building upon the BICCN atlas introduced earlier, recent studies

using single-cell approaches have explored regional and cell-type–specific expression patterns in greater detail. For example, using data from 75 adult donors, one study examined the middle temporal gyrus and reported inter-individual variability in the abundance and gene expression profiles, particularly in deep-layer glutamatergic neurons and microglia [54]. Discrepancies in cell type annotations across the studies shown in Fig. 4 arise from methodological variability in sc-RNA and sn-RNA sequencing workflows. For instance, studies on the human cortex report varying neuronal and glial subtypes due to differences in tissue source (e.g., frozen post-mortem samples in Siletti et al. vs. fresh fetal cortex in Zhu et al.) [52, 55], sequencing platform (e.g., SMART-seq, 10x Chromium, Drop-seq), and developmental stage (adult vs. prenatal). Analytical approaches also differ, including clustering algorithms (e.g., Louvain vs. Leiden), dimensionality reduction techniques, marker gene prioritization, and the integration of spatial transcriptomics. For example, Siletti et al. used whole-brain snRNA-seq to classify broad neuronal groups such as deep-layer corticothalamic neurons; Zhu et al. profiled fetal cortex to define early progenitors; Jorstad et al. applied MERFISH to resolve laminar excitatory and inhibitory neurons; and Johansen et al. used Leiden clustering to identify fine-grained cortical interneuron subtypes [52, 54–56]. These methodological and biological variations underscore the importance of interpreting reported taxonomies within their experimental context and highlight the ongoing need for standardized pipelines in cross-study comparisons.

A comprehensive collection of twenty-one studies has compiled extensive single-cell datasets from both developing and adult brains in humans, NHPs, and mice [52–72]. The list of all brain cell types in NHPs and mice are presented in Supplementary Tables 4, 5, and 6. Figure 4 summarizes a synopsis of ten studies that have identified diverse brain cell types within the human brain. These studies have culminated in the creation of a human brain atlas, comprising over 3000 cell types, and offering insights into their locations and functions at different developmental stages. The proposed taxonomies and representative specimens for mammalian brain cell types will serve as a fundamental reference framework for comparative research across different species. The proposed taxonomies and representative specimens, many of which have emerged from BICCN and the broader BICAN ecosystem, now serve as a fundamental reference framework for comparative research across species.To further contextualize the diversity illustrated in Fig. 4, we provide an overview of key features from each contributing study. Siletti et al. [52] conducted large-scale snRNA-seq across 106 post-mortem adult human brain regions, defining over 3000 transcriptomically distinct cell types, including deep-layer excitatory neurons and specialized glial populations [52]. Zhu et al. [55] employed droplet-based scRNA-seq on fresh fetal cortex samples, identifying early progenitor populations such as excitatory neuron fetal-early and intermediate progenitor cells. Jorstad et al. (2023) combined high-depth scRNA-seq with MERFISH spatial transcriptomics to delineate laminar neuron subtypes—including L2/3 intratelencephalic neurons, chandelier cells, and somatostatin-expressing interneurons—in the middle temporal gyrus.

Johansen et al. [54] applied snRNA-seq coupled with Leiden clustering to classify fine-grained excitatory and inhibitory neuron subtypes in the adult cortex, such as L6 intratelencephalic Car3 neurons and SST-Chodl interneurons. Velmeshev et al. [71] profiled prenatal human cortex samples to identify early neurodevelopmental populations, including dorsal and ventral radial glia and excitatory neurons [71]. Ament et al. [73] focused on cerebellar cell diversity, highlighting granule neurons, Bergmann glia, and immune populations such as microglia and T cells. Kim et al. [66] profiled the developing thalamus, tracing progenitor cell trajectories and identifying temporally restricted neural precursors [73]. Tian et al. [69]
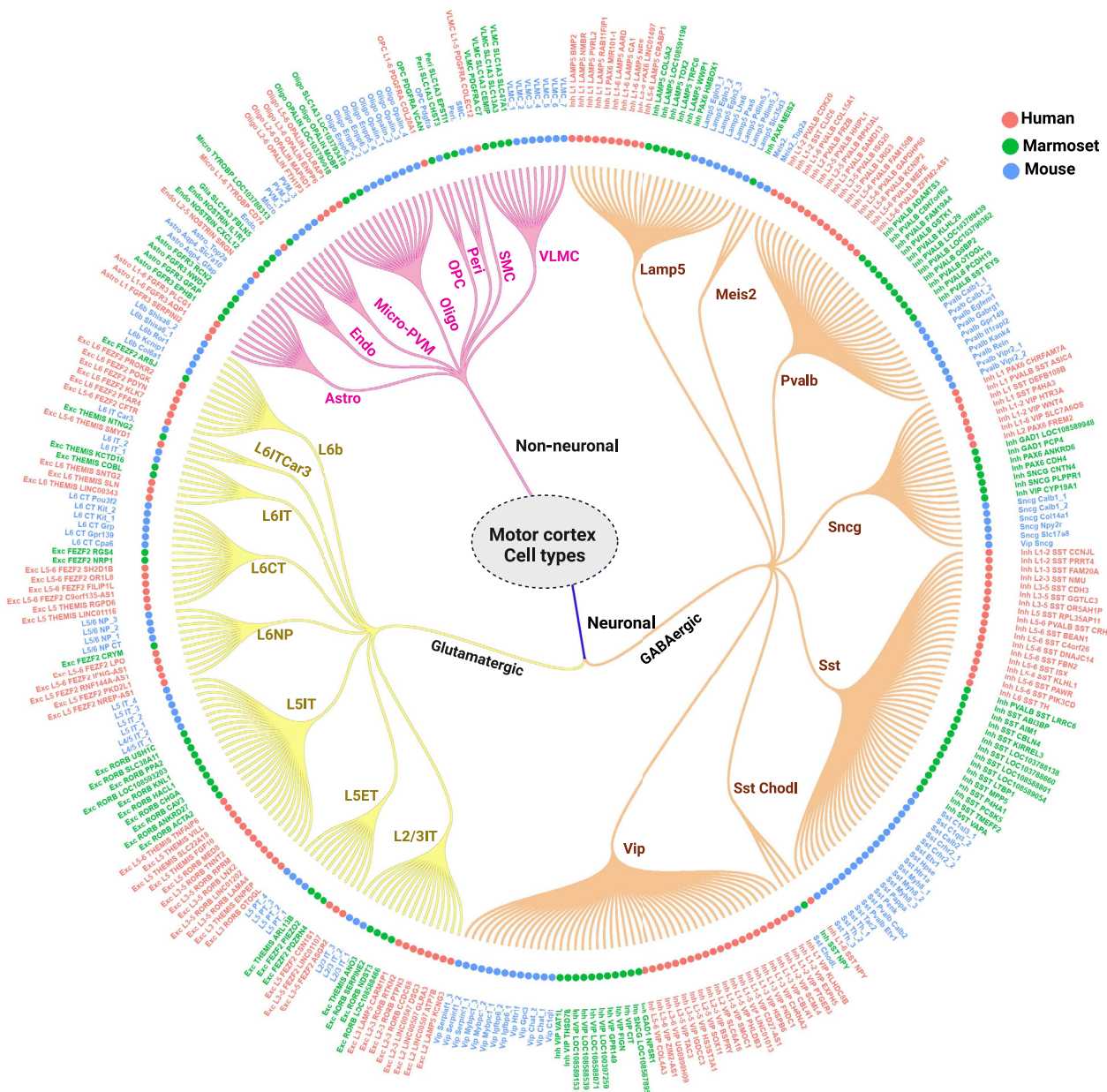
Fig. 3 Motor cortex cell type taxonomy. Circular dendrogram depicting primary motor cortex cell type classification [50]. Cell-type relationships were modelled using single-cell transcriptomic and epigenomic data from the BRAIN Initiative Cell Census Network (BICCN) study (PMID: 34616075), which profiled the primary motor cortex in humans, marmosets, and mice. Hierarchical structure was derived from curated parent–child relationships and node metadata (e.g., species, cell type annotations, proportions) provided in Supplementary Table 2. The directed graph was constructed using the **igraph** R package and visualized as a circular dendrogram using **ggraph**, employing a dendrogram layout optimized for tree structures. Node labels were radially aligned, and diagonal curved edges illustrate branching hierarchy. Species-specific cell types are distinguished by color (Human, Marmoset, Mouse), and additional attributes are visualized using a Viridis colormap. Cluster proportions represent the relative abundance of each neuronal or non-neuronal population. This figure highlights the cross-species conservation and diversity of cortical cell types in the primary motor cortex.

created a cross-regional, multimodal brain atlas integrating snRNA-seq and epigenomic data, revealing distinct cortical, hippocampal, and cerebellar populations [69]. Finally, Li et al. [60] combined chromatin accessibility (ATAC-seq) and transcriptomic data to define conserved and divergent cell types across human, macaque, and mouse brains, identifying key neuronal markers including FOXP2, PVALB, and SST [60]. Together, these studies illustrate how technical, biological, and computational variables contribute to differences in reported brain cell taxonomies.

Moreover, comparative studies using scRNA-seq have illuminated neurogenic trajectories across species, offering insights into the regional and temporal differences in brain circuit formation and maturation. For instance, comparative analyses in NHPs and humans have highlighted conserved aspects of neuronal development alongside species-specific differences in oligodendrocyte maturation [74]. These findings emphasize the importance of cross-species comparisons in understanding neurodevelopmental processes. A notable example of human-specific genetic regulation involves ARHGAP11B, a gene associated with cortical
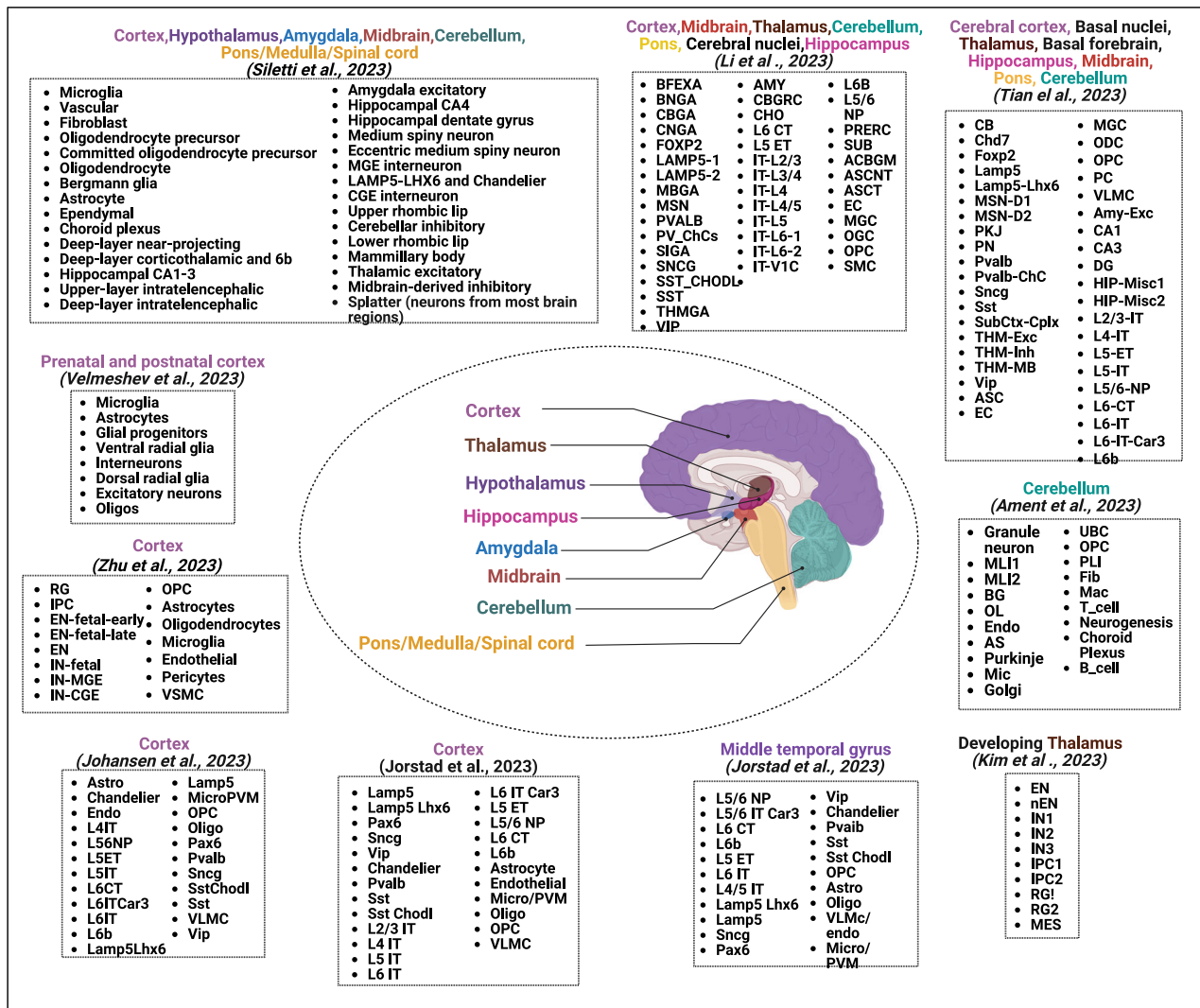
Cortex, Hypothalamus, Amygdala, Midbrain, Cerebellum, Pons/Medulla/Spinal cord
(Siletti et al., 2023)

- Microglia
- Vascular
- Fibroblast
- Oligodendrocyte precursor
- Committed oligodendrocyte precursor
- Oligodendrocyte
- Bergmann glia
- Astrocyte
- Ependymal
- Choroid plexus
- Deep-layer near-projecting
- Deep-layer corticothalamic and 6b
- Hippocampal CA1-3
- Upper-layer intratelencephalic
- Deep-layer intratelencephalic
- Amygdala excitatory
- Hippocampal CA4
- Hippocampal dentate gyrus
- Medium spiny neuron
- Eccentric medium spiny neuron
- MGE interneuron
- LAMP5-LHX6 and Chandelier
- CGE interneuron
- Upper rhombic lip
- Cerebellar inhibitory
- Lower rhombic lip
- Mammillary body
- Thalamic excitatory
- Midbrain-derived inhibitory
- Splatter (neurons from most brain regions)

Cortex, Midbrain, Thalamus, Cerebellum, Pons, Cerebral nuclei, Hippocampus
(Li et al., 2023)

- BFEXA
- BNGA
- CBGA
- CNGA
- FOXP2
- LAMP5-1
- LAMP5-2
- MBGA
- MSN
- PVALB
- PV_ChCs
- SIGA
- SNCG
- SST_CHODL
- SST
- THMGA
- VIP
- AMY
- CBGRC
- CHO
- L6 CT
- L5 ET
- IT-L2/3
- IT-L3/4
- IT-L4
- IT-L4/5
- IT-L5
- IT-L6-1
- IT-L6-2
- IT-V1C
- L6B
- L5/6
- NP
- PRERC
- SUB
- ACBGM
- ASCNT
- ASCT
- EC
- MGC
- OGC
- OPC
- SMC

Cerebral cortex, Basal nuclei, Thalamus, Basal forebrain, Hippocampus, Midbrain, Pons, Cerebellum
(Tian el al., 2023)

- CB
- Chd7
- Foxp2
- Lamp5
- Lamp5-Lhx6
- MSN-D1
- MSN-D2
- PKJ
- PN
- Pvalb
- Pvalb-ChC
- Sncg
- Sst
- SubCtx-Cplx
- THM-Exc
- THM-Inh
- THM-MB
- Vip
- ASC
- EC
- MGC
- ODC
- OPC
- PC
- VLMC
- Amy-Exc
- CA1
- CA3
- DG
- HIP-Misc1
- HIP-Misc2
- L2/3-IT
- L4-IT
- L5-ET
- L5-IT
- L5/6-NP
- L6-CT
- L6-IT
- L6-IT-Car3
- L6b

Prenatal and postnatal cortex
(Velmeshev et al., 2023)

- Microglia
- Astrocytes
- Glial progenitors
- Ventral radial glia
- Interneurons
- Dorsal radial glia
- Excitatory neurons
- Oligos

Cortex
(Zhu et al., 2023)

- RG
- IPC
- EN-fetal-early
- EN-fetal-late
- EN
- IN-fetal
- IN-MGE
- IN-CGE
- OPC
- Astrocytes
- Oligodendrocytes
- Microglia
- Endothelial
- Pericytes
- VSMC

Cerebellum
(Ament et al., 2023)

- Granule neuron
- MLI1
- MLI2
- BG
- OL
- Endo
- AS
- Purkinje
- Mic
- Golgi
- UBC
- OPC
- PLI
- Fib
- Mac
- T_cell
- Neurogenesis
- Choroid Plexus
- B_cell

Cortex
Thalamus
Hypothalamus
Hippocampus
Amygdala
Midbrain
Cerebellum
Pons/Medulla/Spinal cord

Cortex
(Johansen et al., 2023)

- Astro
- Chandelier
- Endo
- L4IT
- L56NP
- L5ET
- L5IT
- L6CT
- L6ITCar3
- L6IT
- L6b
- Lamp5Lhx6
- Lamp5
- MicroPVM
- OPC
- Oligo
- Pax6
- Pvalb
- Sncg
- SstChodl
- Sst
- VLMC
- Vip

Cortex
(Jorstad et al., 2023)

- Lamp5
- Lamp5 Lhx6
- Pax6
- Sncg
- Vip
- Chandelier
- Pvalb
- Sst
- Sst Chodl
- L2/3 IT
- L4 IT
- L5 IT
- L6 IT
- L6 IT Car3
- L5 ET
- L5/6 NP
- L6 CT
- L6b
- Astrocyte
- Endothelial
- Micro/PVM
- Oligo
- OPC
- VLMC

Middle temporal gyrus
(Jorstad et al., 2023)

- L5/6 NP
- L5/6 IT Car3
- L6 CT
- L6b
- L5 ET
- L6 IT
- L4/5 IT
- Lamp5 Lhx6
- Lamp5
- Sncg
- Pax6
- Vip
- Chandelier
- Pvaib
- Sst
- Sst Chodl
- OPC
- Astro
- Oligo
- VLMc/endo
- Micro/PVM

Developing Thalamus
(Kim et al., 2023)

- EN
- nEN
- IN1
- IN2
- IN3
- IPC1
- IPC2
- RG!
- RG2
- MES

Fig. 4 Compilation of human brain cell type studies. Comprehensive representation of 11 studies identifying diverse brain cell types within the human brain. A collection of papers published in Science, Science Advances, and Science Translational Medicine by the NIH's BRAIN Initiative – Cell Census Network (BICCN) presents a large-scale, multi-omics analysis of human brain cell types. Figure created using BioRender.com.

expansion in humans. Dysregulation of ARHGAP11B has been linked to autism-related macrocephaly, highlighting its role in neurodevelopment [75]. Additionally, in neurodegenerative conditions like Alzheimer's disease, hyperreactive microglia exacerbate neurotoxic inflammation [20], contributing to disease progression. These instances illustrate how evolutionary adaptations in brain cell types and circuits may confer cognitive advantages but also predispose the human brain to specific neurodevelopmental and neurodegenerative disorders. In the next section, we will delve into how disruptions in these specialized cell types and circuits further drive these pathologies.

NEURODEVELOPMENTAL AND NEURODEGENERATIVE DISORDERS

Brain connectivity is shaped by both genetic and environmental factors, which begins during embryonic development and continues through young adulthood. Disruptions in these processes contribute to neurodevelopmental disorders (NDDs), while neurodegenerative diseases (NDs), involve progressive neuronal loss and cognitive decline. Recent research has increasingly focused on identifying the specific brain cell types involved in these conditions, with particular attention to the unique molecular and cellular features of the human brain that may predispose individuals to these disorders.

Neurodevelopmental disorders

Neurodevelopmental disorders (NDDs) encompass a diverse range of conditions, including ASD, epileptic encephalopathy, and intellectual disabilities (IDs). These disorders are closely linked to disruptions in early neurodevelopmental processes, with genetic factors playing a central role in their pathogenesis [76–79].

ASD is characterized by deficits in social interaction and communication. scRNA-seq studies have shown that ASD-associated genes are enriched in specific cell types during development, particularly in mid-fetal projection neurons of the PFC and motor cortex [80]. A key pathological feature of ASD is an imbalance in excitatory/inhibitory (E/I) circuits, with downregulated genes in excitatory neurons and upregulated genes in glial cells [81]. Further integrative analyses of ASD-related variants using single-cell transcriptomes have revealed distinct expression patterns in both neuronal and non-neuronal subtypes, emphasizing the spatiotemporal specificity of gene regulation during development [82].

Table 1. Neurodevelopmental and Neurodegenerative diseases and their associated brain cell types.

Disorders	Key altered cell types	Description	Article type	PMID
Alzheimer's Disease	Microglia, astrocytes, neurons	Single-cell RNA-seq neuroinflammation	Analysis	36090352
	Microglia, astrocytes, neurons	scRNA-seq of AD brain inflammation	Analysis	36090352
	Microglia, astrocytes	Single-cell RNA + ATAC in AD	Analysis	38345145
Autism Spectrum Disorder	Serotonergic neurons, GABAergic interneurons, cerebellar neurons	Rodent genetic models in ASD	Review	24290383
	Excitatory neurons (upper-layer), microglia	snRNA-seq of postmortem ASD brains	Analysis	31097668
	Microglia, astrocytes, oligodendrocytes, neurons	Multi-omic single-cell transcriptomics in ASD	Analysis	36945369
	Multiple neurons and glia	Genetics to neurobiology of ASD	Review	25464374
	Neurons, microglia	Transcriptomic and epigenetic profiling	Analysis	36323788
	Various brain cell types	Computational modeling of ASD genetics	Analysis	33519924
	Cortical neurons, microglia	Single-cell genomics of ASD	Analysis	33214565
	Excitatory and inhibitory neurons	Single-cell transcriptomics in ASD	Analysis	35739273
	Neurons, microglia, astrocytes	Multi-modal single-cell RNA + ATAC sequencing	Analysis	38699615
	Neurons and glia	Genetics and molecular pathways in ASD	Review	25464374
	Neurons, microglia	Transcriptomic profiling in ASD	Analysis	34802461
	Multiple brain cell types	Single-cell multi-omics in ASD	Analysis	38419654
	Cortical neurons, microglia	Single-cell genomics in ASD	Analysis	33214565
	Excitatory and inhibitory neurons	Single-cell transcriptomics in ASD	Analysis	35739273
	Neurons, microglia, astrocytes	Multi-modal single-cell RNA + ATAC sequencing	Analysis	38699615
	Excitatory neurons, microglia	Transcriptomic profiling in ASD	Analysis	32439845
	Neurons, microglia	Transcriptomic profiling in ASD cortex	Analysis	34802461
	Multiple brain cell types	Multi-modal single-cell multi-omics in ASD	Analysis	38419654
	Neurons, microglia, astrocytes	Multi-modal scRNA + ATAC sequencing	Analysis	38699615
	Cortical neurons, microglia	Single-cell genomics in ASD	Analysis	33214565
	Excitatory and inhibitory neurons	Single-cell transcriptomics in ASD	Analysis	35739273
	Excitatory neurons, microglia	Transcriptomic profiling in ASD	Analysis	32439845
	Neurons, microglia	Multi-omics single-cell RNA + epigenomics	Analysis	38391931
	Cortical excitatory neurons	Single-cell RNA-seq in ASD	Analysis	27940202
	Microglia, neurons	Single-cell transcriptomics in ASD	Analysis	35338313
	Microglia, astrocytes	snRNA-seq and multi-omics in ASD	Analysis	34888832
	Excitatory neurons, microglia, astrocytes, oligodendrocytes, interneurons	Single-cell RNA-seq enrichment ASD genes	Analysis	26858593
	Excitatory neurons, microglia, astrocytes, oligodendrocytes, interneurons	Single-cell RNA-seq study on mouse/human brain, ASD gene enrichment	Analysis	26858593
Bipolar Disorder	Excitatory neurons, inhibitory neurons	snRNA-seq study of human cortex	Analysis	31031006
	Excitatory neurons, inhibitory neurons	snRNA-seq of human cortex	Analysis	31031006
Schizophrenia	Cortical interneurons, excitatory neurons	Postmortem snRNA-seq of schizophrenia	Analysis	30550949
	Cortical interneurons, excitatory neurons	Postmortem snRNA-seq in schizophrenia	Analysis	30550949
	Cortical neurons, interneurons	snRNA-seq in schizophrenia	Analysis	37321420
	Excitatory neurons, interneurons	snRNA-seq data on schizophrenia	Analysis	37121366
	Cortical neurons, interneurons	Single-nucleus RNA-seq in schizophrenia	Analysis	29785013
Huntington's Disease	Medium spiny neurons	Transcriptomic profiling of Huntington's	Analysis	28522972
	Medium spiny neurons, microglia	Single-cell transcriptomics uncover early glial and neuronal alterations in HD progression.	Analysis	33593693
	Striatal neurons, microglia	Epigenetic and transcriptomic analysis identifies gene expression changes in HD brains.	Analysis	31316211
	Medium spiny neurons	Single-nucleus RNA-seq reveals selective vulnerability of neuronal subtypes in HD.	Analysis	32736085

Table 1. continued

Disorders	Key altered cell types	Description	Article type	PMID
Parkinson's Disease	Dopaminergic neurons, microglia	Multi-omics snRNA-seq in Parkinson's	Analysis	37773446
	Dopaminergic neurons, astrocytes, microglia	Review discussing PD pathogenesis including roles of glial cells and neuron-glia interactions.	Review	31437219
	Dopaminergic neurons, oligodendrocytes	Single-nucleus RNA-seq identifies transcriptional alterations in specific brain cell types in PD.	Analysis	33188239
	Dopaminergic neurons, microglia	Transcriptomic profiling of midbrain neurons reveals selective vulnerability in PD.	Analysis	32053786
	Dopaminergic neurons, astrocytes, microglia	Neuroinflammation-focused review highlighting astrocyte and microglia contributions to PD.	Review	34072062

Ins Inhibitory neurons, *MGE* Medial ganglionic eminence, *CGE* Caudal ganglionic eminence, *RG* Radial glia, *IPCs* Intermediate progenitor cells, *OPC* Oligodendrocyte precursor cell.

Epileptic encephalopathy, characterized by recurrent seizures and cognitive impairment, has also been studied using single-cell transcriptomics. Changes in gene expression across different neuronal subtypes, particularly in interneurons such as basket and chandelier cells, have been identified, implicating them in seizure initiation and propagation [83]. Additional investigations in epilepsy patients have uncovered transcriptomic disparities in various neuronal subtypes [84]. In temporal lobe epilepsy (TLE), snRNA-seq has identified a hybrid glial population with features of both reactive astrocytes and oligodendrocyte precursor cells, contributing to the pathological process [85].

Intellectual Disability (ID) is marked deficits in cognitive and adaptive behaviors, was traditionally studied through neuronal morphological changes. However, recent findings highlight the regulatory role of astrocytes in neural development [86]. Gene sequencing in ID patients reveals that many ID-related genes are predominantly expressed in astrocytes, rather than neurons [87, 88]. Fragile X Syndrome (FXS), a common inherited form of ID and ASD, has been investigated using scRNA-seq, revealing cell type-specific transcriptomic alterations that disrupt core functional processes, particularly in neurons [89].

Neurodegenerative diseases

Neurodegenerative diseases (NDs) are progressive conditions affecting the CNS, characterized by the gradual loss of neurons. Single-cell transcriptomic approaches have been instrumental in unraveling the cellular and molecular mechanisms underlying these diseases, shedding light on how subtle gene expression changes contribute to disease progression.

Parkinson's Disease (PD) is primarily characterized by the loss of dopaminergic neurons and α-synuclein aggregation. Recent studies combining scRNA-seq with immunofluorescence analysis of the nigrostriatal pathway have identified microglial abnormalities in the midbrain, suggesting a broader cellular involvement in PD beyond dopaminergic neuron loss [90]. Post-mortem transcriptomic analyses have further linked PD risk variants to neuron- and microglia-specific genes, highlighting the role of neuroinflammation in disease progression [91].

Alzheimer's Disease (AD), the most common neurodegenerative disorder, characterized by progressive cognitive decline, affects a wide range of cell types. scRNA-seq studies in AD patients have revealed widespread transcriptional changes, with downregulated genes in excitatory and inhibitory neurons and upregulation in astrocytes, microglia, and oligodendrocytes [92]. These findings have been consistent across studies investigating the prefrontal and entorhinal cortices, highlighting the critical role of glial cells in disease progression [93].

Huntington's Disease (HD) primarily affects projection neurons in the striatum. Transcriptomic analyses of post-mortem HD brains have identified high expression of metallothionein (MT) genes in astrocytes, suggesting a neuroprotective response during disease progression [94]. Amyotrophic Lateral Sclerosis (ALS) presents with heterogeneity in both clinical manifestations and genetic underpinnings. scRNA-seq studies of ALS mouse brainstem samples have shown significant transcriptomic changes in inflammation, stress response, neurogenesis, and synaptic organization pathways [95]. Further studies on degenerating motor neurons from ALS patients have identified disrupted transcriptional networks, offering insights into ALS-specific disease mechanisms [96].

A compiled list of cell types associated with various disorders, based on analyses of published studies, is presented in Table 1. Collectively, these findings highlight the significance of integrating mechanistic insights into clinical frameworks. Longitudinal studies tracking aging and disease trajectories offer a promising approach to bridging the gap between molecular discoveries and therapeutic advancements.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

The advent of single-cell transcriptomics has profoundly transformed our understanding of brain cell diversity, providing unprecedented resolution into the molecular and cellular mechanisms underlying neural development, function, and disease. By resolving the molecular profiles of individual cells, this technology has revealed the critical links between genetic regulation, cellular behavior, and neurological disorders. These insights are not only refining our classification of brain cell types but are also unveiling previously unrecognized cellular vulnerabilities that may serve as therapeutic targets.

Looking forward, the integration of multi-omics approaches—transcriptomics, epigenomics, proteomics, and metabolomics—will be pivotal to unravel the complex regulatory networks governing brain cell function and disease. Spatial transcriptomics will further refine our ability to map neural circuits at subcellular resolution, bridging the gap between molecular identity and anatomical connectivity. Concurrently, advances in computational modeling and artificial intelligence (AI) will enhance the integration of vast datasets, enabling precise predictions of cellular behaviors and disease trajectories.

Comparative cross-species analyses will remain instrumental in distinguishing evolutionarily conserved molecular programs from human-specific adaptations, shedding light on the genetic and cellular innovations that underlie higher cognitive functions. Future research will likely elucidate how species-specific gene regulation influences neuronal connectivity, synaptic plasticity,

and cognition. Furthermore, single-cell and single-nucleus transcriptomics will facilitate longitudinal studies, enabling dynamic tracking of cellular changes across developmental stages, aging, and disease progression.

To bridge the gap between molecular discovery and clinical application, experimental validation using high-throughput CRISPR-based functional screens, brain organoids, and advanced in vivo models will be crucial. These approaches will enable precise dissection of disease-associated pathways at the level of specific cell types, paving the way for targeted interventions. By leveraging these technological advancements, neuroscience is poised to uncover fundamental principles of brain organization and function. This progress not only promises to deepen our understanding of human brain complexity but also holds immense potential for developing transformative therapies for neurological and psychiatric disorders, ultimately improving patient outcomes.

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AUTHOR CONTRIBUTIONS

AS and MU conceived the study. AS, BB, NN, HA, ZS, and MU performed data curation from literature and various databases. AS, BB, BKB, MWS, RK, BC, HTB, and MU contributed to writing the manuscript. AS, BB, and MU worked on the figures and tables.

COMPETING INTERESTS

The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Mohammed Uddin.

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