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Brain single-cell transcriptomic atlas reveals neurodiversity and disease-specific glial cell types across regions and developmental stages

In Gyeong Koh[1,2], Jihae Lee[3], Seoyeon Kim[1,2], and Joon-Yong An[1,2,3,4,*]

[1]*Department of Integrated Biomedical and Life Science, Korea University*
[2]*BK21FOUR R&E Center for Learning Health Systems, Korea University*
[3]*School of Biosystem and Biomedical Science, College of Health Science, Korea University*
[4]*Transdisciplinary Major in Learning Health Systems, Department of Healthcare Sciences, Graduate School, Korea University*
**Corresponding author: joonan30@korea.ac.kr*

The brain, the most intricate organ in the human body, consists of various cell types exhibiting unique characteristics and functions specific to regions during development. Recent single-cell RNA-sequencing (scRNA-seq) studies in the brain have revealed these complexities but often disregarded donor diversity such as regions, ages, etc. Thus, much remains unknown about the characteristics of diverse cell types, especially comparisons between cortical and subcortical regions. To address this, we collected 1,516 scRNA-seq profiles of the human brain from 28 datasets and 313 individuals ranging from neonatal to late adult stages, with harmonized metadata. We accounted for the diversity in sex, region, and disease states covering neuropsychiatric, neurodegenerative, neurodevelopmental, and non-neurological diseases. We integrated the data into a comprehensive brain cell atlas with over 4 million cells encompassing more than 24 anatomical regions. We initially performed coarse-level annotation for a subset of the cells with major cell types. We then used deep-learning tools to assign cell types to all cells and re-integrated them for each cell type, leading to more granular annotations. This approach allowed us to define detailed and rare cell types, discovering previously undescribed ones. Neuronal cell types exhibited region specificity, particularly in subcortical regions such as the thalamus, brainstem, basal ganglia, cerebellum, and hippocampus. This region specificity was more pronounced in excitatory neurons, while in inhibitory neurons, we identified a rare cell type known as Neurogliaform cells. These cells were found exclusively in the cortex and hippocampus, with distinct features that vary depending on the brain region. Furthermore, several glial cell types were associated with disease states. For instance, specific oligodendrocyte cell types were associated with dementia and Parkinson's disease, highlighting their role in neurodegenerative disorders. This large-scale brain cell atlas with detailed annotations

identifies rare and disease-specific cell types across regions and developmental stages, providing a valuable resource for understanding the cellular complexity of the human brain.