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Single-cell Analysis of Prefrontal Cortex Reveals Cell Specific Accelerated Aging in People with HIV-1

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Background: A comorbidity of substance use disorder is HIV-1. We hypothesized that accelerated aging will be observed in dorsolateral prefrontal cortex (DLPFC) of people living with HIV-1 (PWH). We analyzed DLPFC biopsies from six PWH and nine people without HIV-1 (PWOH). We examined cell-type specific transcriptomic overlap between HIV-1 and aging, defined as the difference between donors aged below 50 and donors aged over 50.

Methods: Samples were profiled using single-nuclei RNA-Seq. Data were processed using Scanpy. Differentially expressed genes were derived using MAST. We used CellChat to infer cell-cell communication, and assessed DEGs overlap via hypergeometric test.

Results: We identified 22 cell types, based on Allen Brain Reference. Overlap with aging signatures varied across cell types. For HIV-1 up-regulated genes, we observed strong overlap in Interneurons (IT) ($p<10\text{-}300$) and Microglia ($p<10\text{-}41$). In IT, commonly induced genes enriched for neurogenesis, including GRM7, EFNA5, and AGBL4. In Microglia, commonly induced genes enriched for defense response, including PARP14, FYB1, and CTSC. We determined that global decrease in cell-cell communication is common to HIV-1 and aging. Communication pathways decreased in both conditions include Glutamate, neurexin presynaptic cell adhesion proteins (NRXN), and GABA-A. Decreased communication includes as either sources or targets cell types 5/6 NP, and IT excitatory neurons L3/4. We observed a common reduction in communication between ligand Glu-SLC1A1 and receptors GRIA2, GRIK2, GRIA3, GRIK4.

Conclusions: We identified aging related transcriptional profiles in specific cell types and cell-cell communication in DLPFC of PWH, and will validate our findings in additional samples.