Leveraging scRNA-Seq Profiles of Psychiatric Disorders to Identify Disorder-Associated Gene Co-Expression Modules

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Psychiatric disorders, including schizophrenia (SCZ) and bipolar disorder (BD), are leading causes of global disability. The development of effective therapeutics is challenged by the complexity and highly polygenic nature of these disorders. Recently, single-cell transcriptomic profiling of large cohorts of psychiatric postmortem donors provides new avenues to reveal molecular mechanisms relevant to drug development. However, single-cell measurements often contain considerable experimental noise due to differences in sequencing methods between different institutions. To overcome this challenge, I employed scdemon (single-cell decorrelated module networks), a framework to identify gene co-expression modules that allows us to share and normalize statistical power across groups of genes with correlated expression patterns. In this study, I applied scdemon to a dataset of 506,690 single nuclei from the prefrontal cortex of 72 postmortem donors with clinical diagnoses of SCZ, BD, and matched neurotypical controls. Our 124 identified gene modules across six major cell types were highly expressed in functions including synaptic transmission, neurodevelopment, and metabolic processes. While some modules were identified recurrently across cell types (e.g. those differentially expressed in transcriptional regulation, etc.), others were identified in specific cell types. Additionally, I analyzed modules' differential expression across donor diagnostic status and biological sex. Select modules exhibited coordinated differential expression in both SCZ and BD, consistent with the shared genetic architecture of these disorders. Together, these results provide a foundation for interpreting the molecular etiology of psychiatric disorders.

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