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Inferring Memory-related Regulatory Modules in Engram Cells by Deep-learning and scRNA-seq Data

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To understand the detailed molecular mechanisms of memory formation in engram cells is one of the most fundamental questions in neroscience and computational system biology. Recent single-cell RNA-seq (scRNA-seq) techniques have allowed us to explore the sparsely activated engram ensembles, enabling access to the molecular mechanisms that underlie experience-dependent memory formation and consolidation. However, the absence of specific and powerful computational methods to detect memory-related genes (modules) and their regulatory relationships in the scRNA-seq datasets has strictly limited the analysis of underlying mechanisms and memory coding principles in mammalian brains. Here we designed a deep-learning method to detect memory-related gene modules in scRNA-seq datasets, and a deep learning method to infer causal regulatory relationships with gene modules. We applied them to snRNA-seq datasets of TRAP; Ai14 mouse neurons with and without fear memory and detected not only known memory-related genes, but also the modules and potential causal regulations. Our results provided novel regulations within an interesting module including Arc, Bdnf, Creb, Dusp1, Rgs4 and Btg2. Overall, our methods provide a series of computational tools for processing scRNA-seq data and delineate the regulation mechanisms underlying remote memory formation. The detected gene modules may provide potential targets and strategies for treatment of memory loss in neuron degenerative diseases. The methods can also be used to process general scRNA-seq datasets that are generated from case versus control studies.