Title: Inputs Drive Cell Phenotype Variability

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What is the significance of the extensive variability observed in individual members of a single cell phenotype? This question is particularly relevant to the highly differentiated organization of the brain. In this study we analyze the in vivo variability within a neuronal phenotype in terms of synaptic input type. We developed a large-scale dataset from several hundred single neurons from a brain nucleus using high throughput gene expression data. The neurons analyzed were selected on the basis of their specific synaptic input-types. Our results show a surprising structure with respect to input-types such that neuronal variability was organized as a continuum of sub-phenotypes and associated gene regulatory modules. The results also reveal correlations between these regulatory modules and specific cellular states that are stratified by the synaptic input-type. Additionally the phenotype gradient and correlated modules were maintained across individual subjects. Finally, we show that these inputs shape a dynamic landscape of molecular states enabling distinct state-dependent functional responses of neurons to a perturbation within a phenotype. We interpret the phenotype gradient as arising from an analog tuning of underlying regulatory networks driven by distinct inputs to individual cells.

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