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Opinion Article

Spatial Cell Type Enrichment in Brain Connectivity

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DESCRIPTION

A fundamental question in neuroscience is whether and how the brain's molecular, cellular and cytoarchitectonic properties govern its inter-regional structural connectivity. Several recent studies have leveraged spatial transcriptomic data to infer the mouse mesoscale connectome with high accuracy, indicating that there is a strong biological link between whole-brain gene expression and inter-regional connectivity. However, despite the fact that cells are the fundamental biological units forming and maintaining white-matter tracts, the question of whether and which regional cell-type distributions determine patterns of structural connectivity, has received scant attention. Such a link has been previously postulated, but the lack of a comprehensive spatial atlas of cell types in the mouse brain has prevented its direct investigation. Here, we utilize recent advances in whole-brain mapping of a variety of neuronal and non-neuronal subtypes using the Matrix Inversion and Subset Selection (MISS) algorithm to model inter-regional connectivity as a function of regional cell-type composition with various machine learning approaches. Of the different machine learning models we tried, the random forest algorithm was the only method to give excellent performance at predicting both the binary existence and absence of a connection and the connectivity density between region-pairs. Moreover, using feature importance analysis, we found that oligodendrocytes and endothelial cells were the most salient for reconstructing the whole-brain connectome and correlated strongly with several node-level connectome graph metrics. We also found that layer-specific excitatory neurons contributed most for predicting long-range connectivity, while several interneuron subtypes were highly informative for predicting short-range connectivity. Prediction accuracy was similar across two independently sampled sets of cell types, indicating that cell-type distributions are a robust predictor of inter-regional connectivity.

The structural connectome, which represents the density of physical projections between each pair of brain regions and is measured by such techniques as viral tracing and diffusion tensor imaging, is a coarse wiring diagram of the central nervous system. Complex molecular processes during embryonic development encourage the formation of connections between brain regions, and later postnatal pruning results in structural connectomes with a remarkable degree of conservation between healthy individuals. A rigorous exploration of the relationships between gene expression, cell type distributions, and inter-regional connectivity can deepen our understanding of how brain circuits mature during the development of the central nervous system and how they are disrupted in neurodegenerative diseases, among other areas of inquiry. Accordingly, there is strong interest in gaining an understanding of how the gene expression and the cell type composition of each region relate to connectivity. In particular, the correlation between regional gene expression and connectivity is well established in mice and humans, but the methods used to determine this association are mainly correlative or analytic. Additionally, several groups mentioned that connected regions tend to have higher correlated gene expression patterns than regions that are not, which naturally raises the question of whether the connected brain regions share common cell types. However, their methodology has not yet been scaled up to produce a dataset of comparable spatial coverage to the Allen Mouse Brain Connectivity Atlas (AMBCA), which is perhaps the most thorough mesoscale connectome currently available. Therefore, it is not yet clear how distributions of different types of cells the fundamental units of connectivity.

Taken together, our study provides the first demonstration of a link between whole-brain cell-type distributions and the structural connections between regions, and provide a road map for examining this relationship in other species, including humans.

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