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Editorial

Methods for single-cells

The brain is a complex organ composed of many different interacting cell types. To better understand brain function, neuroscientists need to look at how different cells operate in an intricate network. Early data support the classification of brain cell types in broad categories of neurons and glia, but today we know that, even within a particular neuronal or glial population, cells are different from the genetic, molecular, biochemical and functional perspectives. After decades of research, we have learned that different subpopulations of cell types play specialized roles and that such single-cell heterogeneity is critical for the understanding of brain operations. Methods allowing for detailed single-cell examination at different scales from local to brain-wide networks are therefore at the kernel of our current methodological toolbox. In this Special Issue, leading researchers in the field review cutting-edge methods from genomic to functional studies aimed at untangling brain cell-type heterogeneity with an unprecedented level of detail.

The issue opens with a review by Mark Cembroswki on single-cell transcriptomics from the perspectives of next-generation RNA sequencing and high-throughput in situ hybridization (Cembrowski, 2019). He highlights the advances and insights that these complementary methodologies provide into the nervous system. Next, Gozes et al. (2019) illustrate how transcriptomic techniques combined with molecular and imaging technologies can provide a critical foundation for understanding the structure and function of the single-cell cytoskeleton. Understanding cellular heterogeneity is also critical to advance the study of brain disease mechanisms and novel cell therapies, including cell reprogramming. van den Hurk and Bardy (2019) discuss how single-cell genomics help benchmarking and optimizing tissue engineering.

The ability to record the activity of individual brain cells *in vivo* is essential to better relate cellular structure and function. Single-cell recording and labeling of identified cell-types *in vivo* is challenging, but several new approaches now permit the interrogation of neuronal activity in freely moving and head-fixed rats and mice. Cid and de la Prida (2019) review the most successful approaches and provide operational recommendations for optimizing recording and labeling. Next, Valero and English (2019) discuss how single-cells can be targeted in behaving animals by exploiting head-mounted electrode microdrives while Suk et al. (2019) review recent advances in automation of patch-clamp for better ease-of-use, reproducibility, throughput and standardization of single-cell recording techniques.

Currently available methods to manipulate brain activity now allow for the interrogation and manipulation of microcircuits in a cell-type-specific manner. Ferruccio Pisanello and his collaborators review how exploiting unconventional combinations between optics and photonics allows for control and monitoring of physiological phenomena in a single-cell specific fashion (Pisano et al., 2019). Following this thread, Ilan Lampl and his colleagues discuss how whole-cell recordings can be combined with optogenetics or pharmacology to better understand the origin and integration of synaptic inputs on identified single cells (Katz et al., 2019), and Schwarz and Remy (2019) summarize the latest developments in single-cell transsynaptic tracing that permits dissection of neuronal circuit structure and function. Finally, Sauvage et al. (2019) review a palette of methods allowing for monitoring molecular processes that subserve synaptic plasticity and memory consolidation with single-cell resolution.

This Special Issue is timely, as there are currently several institutes and laboratories developing atlases and open access platforms to facilitate the study of the brain with single-cell resolution. These single-cell mapping strategies are combined with several concerted, collaborative efforts to promote technological development and computational approaches toward a multidisciplinary exploration of our more complex organ. Although this collection cannot be exhaustive, we hope that it will increase the interest of the scientific community in this growing field of neuroscience. Understanding the brain at the single-cell level is also bound to advance therapies for devastating disease with a leap forward to precision medicine for disease modification emphasizing commonalities and providing a deep understanding of differences.

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