Forum: Neuroscience

A census of cell types in the brain's motor cortex

An atlas of the cell types found in the motor cortex of the brain has been built using various types of data. Two neuroscientists explain the technological feats that went into the project, as well as the utility of the resource for future research.

Cell census will be a boon for future studies

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The high cell-type diversity of the brain poses an enormous challenge to neuroscience. By building their cell-type census and atlas, the BRAIN Initiative's Cell Census Network (BICCN)[1] will accelerate efforts to unravel how neuronal cell types are defined, how they connect in networks and how they contribute to function.

The BICCN focused on a brain region called the motor cortex, a structure particularly well-suited to such an in-depth investigation. First, it extends neuronal projections directly to many other regions of the motor system and thus acts as a broadcasting device[2,3]; yet, how it interacts with these other regions is poorly understood. Second, the motor cortex controls movement, and so understanding its cell types provides the possibility to link them to function and behaviour. Third, from an evolutionary perspective, its size, cell-type diversity and functions differ considerably across species[2], an aspect the BICCN specifically addressed through studies in mice, marmosets and humans[1,4].

The BICCN flagship paper highlights the main resources and findings generated by this enormous collaborative network[1]. The neuroscientific community will have access to databases containing information about many aspects of different cell types in the motor cortex of different species including their gene expression, the molecular modifications that alter their gene expression, their morphology and their electrophysiological properties. The BICCN consortium has also generated many mouse strains in which key neuronal populations can be specifically targeted by different manipulations — for example, to label them or control their activity[5].

The papers accompanying the flagship paper prove the high utility arising from mining data. Although the numbers of different cell types identified using different methods vary[1], future mining of combinations of the provided data sets could substantially strengthen conclusions on cell-type definitions and enable efforts to understand their function in behaviour.

Cortical neurons have long been known to fall into two main categories: those communicating exclusively with other cortical neurons and those also communicating with neurons outside the cortex. Some of the studies by the BICCN — including those by Matho et al.[5], Peng et al.[6] and Muñoz-Castañeda et al.[7] — serve as entry points for future work to address how cell

types in these categories are embedded and function in local cortical circuits, in loops with other structures in the brain such as the basal ganglia and thalamus and in long-range pathways to other regions of cortex, the brainstem and the spinal cord. Understanding these cell types and their interactions will help us to establish how they contribute to the learning, control and execution of movement, and how actions unfold at the systems level.

The BICCN papers present snapshots of the identities of adult neurons, which, because they are mostly not replaced throughout life, each have their own history. This includes its developmental trajectory to maturation and its individual experience up to its analysis, including modifications during learning and plasticity. Genetic programs during development are central to defining basic properties of neuronal cell types including functional attributes, such as neurotransmitter identity or firing properties as is known from the spinal cord[8].

The genes that constitute these developmental programs can serve as markers of different neuronal types, and work by the BICCN (for example, by Matho et al.[5]) will advance researchers' ability to target marker-defined cell types in mice. Later in life, however, experience influences gene expression and can even lead to a switch in the type of neurotransmitter molecule that a cell releases[9]. Future work should therefore determine the extent to which cell-type diversity reflects changes in gene expression due to experience, including learning and plasticity.

Lastly, the BICCN papers — for example, those by Bakken et al. and Berg et al. — also begin to compare cell types across species[4,10]. This approach will provide insights into which neuronal cell types have evolved from others and which are evolutionarily new 'add-ons', and how they might contribute to evolutionarily novel functions. Such work will be crucial to design cell-type-specific therapies for brain disorders, because, although many principles of circuit function are conserved across species, any such interventions must be tailored to the human brain.

The BICCN papers represent a real treasure trove for future discovery — most notably, for explorations leading to a granular understanding of how the motor cortex helps to control and modulate many forms of movement. Science itself has indeed moved a long way from observations some 150 years ago that electrical stimulation of a region in the cortex can elicit movement[11].

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