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Decoding neuronal diversity in the developing cerebral cortex: from single cells to functional networks

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The neocortex is by far one of the most complex regions of the mammalian brain, characterized by an extraordinary diversity of neuronal and non-neuronal cell types, whose coordinated development and function guarantee the execution of high-order cognitive, sensory, and motor behaviours. Decoding its heterogeneity and understanding the molecular strategies upon which the cerebral cortex is built during development have been at the core of neuroscientists' work for decades. Here, we will focus on the current classification of neuronal types (both excitatory and inhibitory) of the neocortex in light of the insights provided by recent single-cell omic technologies, which have offered — with unprecedented resolution — an extended framework to interpret cortical diversity and its developmental origin. We will cover the impact of neuronal subtype identity on generating specific neuronal networks (neuron-to-neuron interaction), as well as their effect on the development of the non-neuronal populations in the cerebral cortex.

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Introduction

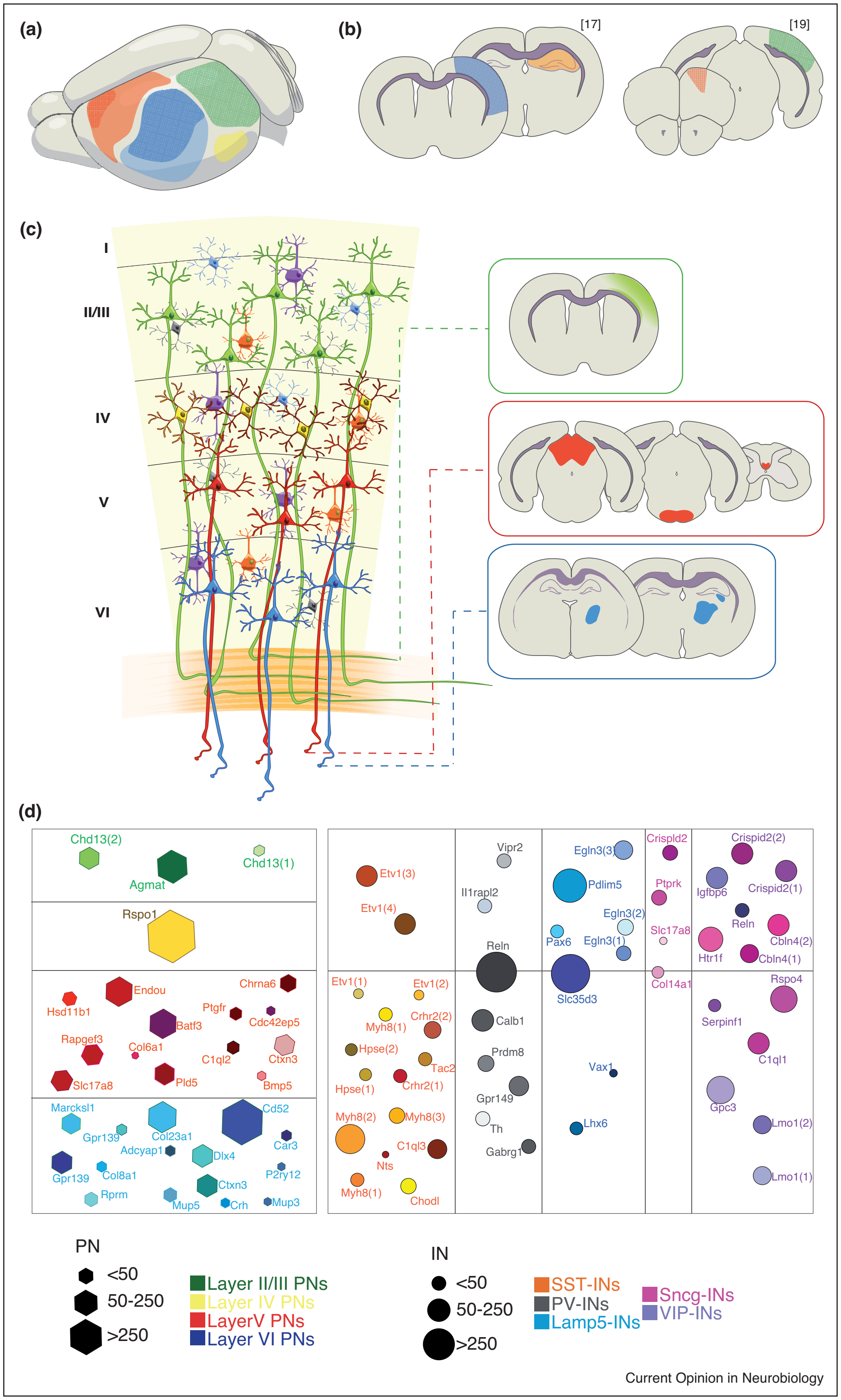
The ability of the mammalian brain to execute sophisticated behaviours — including complex cognitive functions and fine motor and sensory tasks — relies on the evolution of a large variety of specialized neuronal circuits [1]. A highly-elaborated 'jungle' of circuits, which is composed by distinct classes of excitatory and inhibitory neurons, represents a distinctive feature of the cerebral cortex [2]. The challenge of defining such complexity though — by counting and cataloguing its fundamental functional units — has puzzled neuroscientists for over a century. The renowned heterogeneity of the cortex, coupled with its intrinsic inaccessibility (as well as the brain in general) and the limited tolerance of neuronal cells to manipulation, have hampered progress in that direction, leaving the molecular classification of neuronal subtypes a daunting task for long time. The development of reliable and robust protocols for the dissociation and isolation of cortical cells, in combination with the advent of technologies that can simultaneously process large numbers of cells at affordable/limited costs, has revolutionized the field. In this review, we describe the recent advancements on cortical neuronal classification and the unfolding insights into cell-type specific functions. We review the developmental origin of neuronal diversity of both excitatory and inhibitory neurons of the cortex and then conclude discussing how the proper subtype-specific identity of cortical neurons not only influences the assembly of functional networks, but also impacts the developmental programs of the surrounding non-neuronal types, ultimately shaping the overall architecture of the mature cortex.

Parsing neuronal diversity in the cerebral cortex

During evolution, the mammalian neocortex has undergone a very pronounced expansion in its size, surface area, as well as in the output of cells produced during corticogenesis [1,3]. In parallel, it has developed an outstanding diversity of neuronal and non-neuronal subtypes that collectively contribute to its '*supreme dignity and inextricable complexity*', as already anticipated by the visionary neuroscientist Ramon y Cajal in the late 1800s. The larger number of neurons estimated, specifically in the human cerebral cortex, compared to other mammalian species, has been proposed to positively correlate with distinctive complex behaviours and enhanced cognitive capabilities [3]. Despite the species-specific differences — which are clearly emerging also at cellular and molecular levels [4] — the subdivision into specialized areas (Figure 1a), the relative radial thickness, the laminar distribution of the cells (Figure 1c), and the developmental programs underlying corticogenesis are largely shared among all the mammals [1,5].

Neurons and glial cells constitute the two main classes of neocortical cells. Here, we focus on the diversity of neurons, which can be classified in excitatory glutamatergic projection neurons (PNs) and GABAergic inhibitory interneurons (INs) (Figure 1c). Inhibitory INs are

Figure 1



(a) Schematic representation of adult mouse brain areas: motor (red), somatosensory (blue), visual (green) and auditory (yellow). **(b)** Diagram of brain coronal sections highlighting the areas where single cell RNA sequencing has been performed as reported in Zeisel *et al*. [17••] (S1 in blue,