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Whoever contemplates the last 25 years of tremendous progress in developmental neurobiology would be right to describe it as a golden age, and may therefore be tempted to ask the same question raised by the artists of the Renaissance: "What can we do beyond what was already accomplished in the Ancient golden age?". Could it be that all fundamental mechanisms of neural development have been identified and exposed, leaving to the younger generations the painstaking dissection of whatever tiny details were left incompletely uncovered? Well, of course not, as surely as there has been plenty to create and admire beyond the Parthenon, Milo's Venus, or the Odyssey.

Yes, we may indeed have entered an era of post-classical neural development, which gives us access to an unprecedented world of possibilities to challenge the now-established views, and shed light on the many remaining obscure corners of brain development. Because there are many mysteries left to solve in the developing brain, indeed, as the reviews presented in this Issue will demonstrate. And they will also show that, to keep in line with the art metaphor, today's developmental neurobiology does seem to share many features of modern art, in particular the ability to mix and match old and new models and concepts, to reveal complexity through variations on seemingly invariant themes, and to combine unrelated reductionist approaches to reach holistic views.

Neural development is classically thought to involve discrete steps, such as neural induction, regional patterning, cell differentiation and specification, morphogenesis, and finally neural circuit formation and refinement. But while this textbook view makes it easier to represent these complex processes, to teach and learn and think about them, in real life neural development is not a fixed ladder-like structure, but rather emerges from a time-driven continuous flow of events, within which most of the so-called steps are in fact highly intermingled. This will be exemplified by many of the reviews that address multiple mechanisms or steps of development, once separated and now highly integrated.

Another feature that emerges is that most of the authors discuss concepts drawn from several model systems. This comparative approach leads to a more holistic view of development, tightly linked to evolution. It enables the identification of universal mechanisms that can be found across species or brain regions, for instance, or, on the opposite hand, highlight divergent strategies. One can start to grasp how it is that neural circuits share many features across regions, systems or species, but yet display specific, sometimes unique characteristics that allow them to make us what we are, as individuals and as a species.

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Moreover, while there is general acceptance that neural development does stop at some arguable point in time, beyond which the brain starts to function as a mature organ, when exactly this occurs is much less clear, and the answer quite variable depending on the model, substructure, or species considered. Several reviews will examine this point, focusing on how brain structure and function can change beyond the ontogeny of its circuit blueprint, through refinement, plasticity, or regeneration.

Studying neural development as a continuum of intermingled processes has been challenging, yet a new era is starting when revolutionary technology, including single-cell analysis, is primed to make ground-breaking advances in our understanding of not only the diverse cellular composition of the nervous system, but also of the mechanisms that shape and wire this cell diversity, with unprecedented temporal and spatial resolution.

A first set of reviews deal with emerging views on how stem/progenitor cells balance self-renewal and differentiation, through cues that are sometimes already well known and at other times quite surprising. Guillemot and Hassan start with a most classical theme, proneural factors highly conserved throughout the animal kingdom, and discuss recent discoveries of unexpected ways in which these proteins are regulated, in particular novel mechanisms of post-transcriptional control, and of novel roles, such as promoting not only neural differentiation but also the proliferation of stem cells. They also discuss how these factors have become powerful tools for lineage reprogramming from non-neuronal to neuronal cells. Focusing on the cerebral cortex, Delaunay et al. explore how a basic feature of the cell, mitosis, can affect neurogenesis in highly diverse yet specific ways. The shape, polarity, and degree of symmetry of the neural stem/progenitor cell as it divides can profoundly influence the identity of its progeny, although, at the same time, cell division can be surprisingly uncoupled from fate specification. The impact of specific properties of stem cell division is best exemplified by the outer radial glial cells: Ostrem et al. review the latest molecular and cellular findings on this fascinating progenitor cell population of the cortex, with emphasis on their characteristic pattern of mitotic somal translocation, in relation with human brain evolution and disease.

Like cell division, metabolism is a fundamental aspect of cell biology, yet it has been generally considered at best a mere permissive developmental cue. Knobloch and Jessberger discuss recent findings that directly link various metabolic flows, from glycolysis to lipogenesis, to neural stem cell biology and neurogenesis. These new data are likely only the tip of the iceberg for the emerging view of metabolism as a critical hub that integrates developmental cues and neural cell fate decisions.

Time has always been a fundamental coordinate in biology, but how it is encoded and used in neural development has remained quite mysterious compared with our depth of knowledge on space and its role in patterning distinct brain regions. Rossi et al. provide a comprehensive comparative overview throughout species and systems, from fly retina to human cortex, of how time is encoded into lineages to generate ordered cellular diversity. They delineate the elements that appear to be evolutionarily conserved, but also point out that in vertebrates temporal patterning seems to be less deterministic, leaving open the question of whether complementary mechanisms are involved.

Applying a holistic approach to the daunting question of the origin of one of the most diverse neuronal cell types of the brain, the cortical inhibitory

interneurons, Bandler et al. illustrate how temporal patterning, mode of cell division and spatial cues intersect to generate the tremendous diversity of subtypes that we know exist within this neuronal population.

How these themes, both classical and unconventional, contribute to the development and evolution of neural structure and function is the focus of a second set of reviews. Bielen et al.'s discussion of evolutionary divergence in the timing of spatial patterning events, and how this heterochrony may contribute in a major way to the evolution of the vertebrate forebrain, nicely illustrates how variations on a classical theme (subtle changes in the temporal regulation of highly conserved patterning cues) can lead to novelty in evolution. Similarly, Florio et al. discuss how very recent genomic changes leading to novel hominid-specific genes and regulatory elements may have contributed to the rapid evolution of the human cortex, and therefore, of species-specific features of the human brain. Kolodkin and Hiesinger compare the mechanisms controlling the development of the anatomically distinct fly and vertebrate visual systems, pinpointing both highly conserved rules, such as intrinsic self-patterning, and species-specific contingencies, such as higher order laminar and columnar patterning.

How do the processes of morphogenesis and generation of the cellular building blocks of the nervous system contribute to the exquisite precision with which the system is wired to guarantee synaptic connectivity among the correct neuron partners and, ultimately, brain functionality? How do intrinsic cues, activity and experience shape the wiring plan? These are fundamental questions that lie at the core of the principles that shape the development and functionality of the brain. Dasen discusses how the subtype identity of motor neurons in the vertebrate spinal cord affects not only the choice of innervation target but also afferent connectivity by pre-motor and sensory neurons, providing instructive cues for the assembly, function, and evolution of locomotor circuits. Schreiner et al. describe genetic and proteomic techniques that enable the dissection of the mechanisms by which synaptogenesis between defined neuronal partners is controlled, and by which synapse-specific molecular compositions are conferred. Kolodkin and Hiesinger compare and contrast the mechanisms of circuit wiring in flies and vertebrates, discussing how complex neuronal wiring is governed by patterned tissue organization and refined by differential use of adhesion and synaptic molecules. Focusing on the visual system, the authors consider a range of shared principles that may also be relevant to the wiring of other complex neural circuits. Thompson et al. discuss how neuronal activity in the visual system works with molecular cues to instruct the establishment of initial circuit maps, which are then refined by visual experience.

Even after development is complete, neuronal circuits are by no means static entities, and plasticity in neurons and networks rests at the foundation of the nervous system's capacity for learning and memory, and its ability to adapt to changes in sensory experience and after injury. Synapses are controlled not only by neurons, but also by glia, which, as discussed by Stogsdill and Eroglu, continuously interact with neurons to mediate not only synapse formation but also synapse remodeling and plasticity. The authors also discuss the central role of astrocytes and microglia in actively refining circuits, through controlled pruning of synapses, to serve circuit function, a process that relies on close interactions between glia and neurons to provide circuit plasticity "on demand". Beyond astroglia, Herbert and Monk discuss the role of oligodendrocytes and myelin in affecting circuit functionality and plasticity, in particular the feedback mechanisms that control neuron-oligodendrocyte interplay and allow a "creative" use of myelin to diversify circuit function and provide an opportunity for increased plasticity. Dehorter et al. highlight the central role of circuit plasticity conferred by locally-connected inhibitory interneurons of the cerebral cortex, which adapt to changes in circuit activity to modulate its dynamics and plasticity. The authors also present the intriguing argument that the ability to generate new interneurons, via in vivo lineage reprogramming strategies, may provide a source of cells able to integrate into pre-existing circuits to modulate their plasticity, perhaps even in pathological situations.

Adult neurogenesis and related circuit remodeling offer interesting insights into the extent to which adult circuits retain plasticity and the capacity for change. Sailor et al. discuss changes in structural plasticity in the adult brain. Investigation of synaptic plasticity in non-neurogenic circuits connected to neurogenic niches has highlighted the capacity of existing circuits to undergo remodeling in response to the continuous generation of new neurons, unearthing the hidden capacity for structural plasticity of mature circuits directly connected to adult-born neurons. This work raises the question of how plastic adult neurons and circuits can really be, and how adult neurons respond to profound challenges, like traumatic injury. Despite the proven resistance of adult mammalian neurons to grow new long-distance projections, Tedeschi and Bradke highlight recent findings suggesting that the adult CNS may possibly retain the ultimate form of plasticity: the capacity, whether endogenous or exogenously induced, for axon regeneration and neuronal circuit assembly and repair.

We conclude by considering emerging new approaches and transformative technologies that are bound to affect the way we investigate brain development, wiring and plasticity. Llorens-Bobadilla and Martin-Villalba discuss advances in our understanding of the diversity of neural progenitor cells, departing from a model of universal stem

cells and highlighting the roles of niche-derived cues for NSC diversification. Johnson and Walsh describe how single-cell molecular profiling of RNA, DNA and epigenetic states has exponentially progressed in very recent times, and the exciting opportunities offered by the application of this technology to virtually unlimited numbers of single cells. At such unprecedented scale of analysis, classic questions regarding the cellular composition, classification and diversity in the CNS can be answered. We agree with the authors that these technologies make possible reference atlases in which molecular profiling data on individual cells is linked to their spatial brain coordinates: the use of high-throughput single-cell sequencing technology will extend such mapping to millions of cells.

As we hope will be emerging from the reviews in this Special Issue, a Renaissance period of discovery has started, in which transformative experimental approaches promise to provide new insights into the processes that integrate the generation of the extreme cellular diversity and intricate connectivity of the nervous system, and to uncover how activity, experience and disease impinge on neural development and function.