

Development and Arealization of the Cerebral Cortex

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Adult cortical areas consist of specialized cell types and circuits that support unique higher-order cognitive functions. How this regional diversity develops from an initially uniform neuroepithelium has been the subject of decades of seminal research, and emerging technologies, including single-cell transcriptomics, provide a new perspective on area-specific molecular diversity. Here, we review the early developmental processes that underlie cortical arealization, including both cortex intrinsic and extrinsic mechanisms as embodied by the protomap and protocortex hypotheses, respectively. We propose an integrated model of serial homology whereby **intrinsic genetic programs and local factors establish early transcriptomic differences between excitatory neurons destined to give rise to broad “proto-regions,” and activity-dependent mechanisms lead to progressive refinement and formation of sharp boundaries between functional areas.** Finally, we explore the potential of these basic developmental processes to inform our understanding of the emergence of functional neural networks and circuit abnormalities in neurodevelopmental disorders.

The cerebral cortex is responsible for many of the higher level cognitive functions in humans, including language, perception, decision making, and motor planning. Anatomically, the cerebral cortex can be broadly divided into neocortex (or isocortex) and allocortex, which includes structures such as the hippocampus and olfactory cortex and comprises a relatively larger proportion of cortical area in lower mammals, such as mice. Neocortex is defined by the presence, at some point during development, of six distinct anatomical layers parallel to the cortical surface with alternating cell density (layers I, III, and V being relatively cell sparse and layers II, IV, and VI being relatively cell dense). It remains unclear whether the neocortex truly represents a phylogenetically newer anatomic structure (Northcutt and Kaas, 1995), and so the term “isocortex” may be more appropriate.

At the cellular level, the cerebral cortex is composed of approximately 16 billion neurons, accounting for more than 80% of the total brain mass (Azevedo et al., 2009). The astonishing diversity of neuronal types has been appreciated since the days of Santiago Ramon y Cajal, and yet we still lack a comprehensive overview of neuronal diversity in the cerebral cortex, in particular how morphological, molecular, and physiological diversity relates to functional areas of the cortex. Even less is known about the developmental processes that give rise to these diverse cell types. Recent advances in molecular profiling, including those with single-cell resolution, have created the opportunity to revisit these developmental processes at the

level of genes and regulatory pathways (Lein et al., 2017). Here, we review the current evidence and potential mechanisms of cortical arealization with a particular focus on human cortical development, although studies using model organisms are also included.

Manifestations of Cortical Arealization in the Adult

Differences in cortical cytoarchitecture, including abrupt changes in cell number, density, and lamination and the appearance of morphologically distinct cell types, have long been recognized (Brodmann, 1909; Defelipe et al., 1999; von Economo and Koskinas, 1925). These histological differences have been used to define anatomical areal subdivisions and often correspond to specialized functional areas (Bayer and Altman, 1991; Elston, 2003; Hof and Nimchinsky, 1992). Across the cortex, the density of neurons varies by as much as two-fold, primarily due to an increase in the density of upper (“supragranular”) cortical layer neurons in the caudal and medial areas (Charvet et al., 2015). Several of the most distinct area-specific lamination patterns are highlighted in Figure 1A. One of the most striking examples is the abrupt transition from secondary visual cortex to primary visual cortex, where a single layer IV abruptly splits into three sublayers. In other cortical areas, including the primary motor cortex, layer IV is not apparent in histological sections. Similarly, the insular cortex shows a unique lamination pattern in which layer VI is split into sublaminae, which are continuous with the adjacent claustrum (Watson and Puelles,



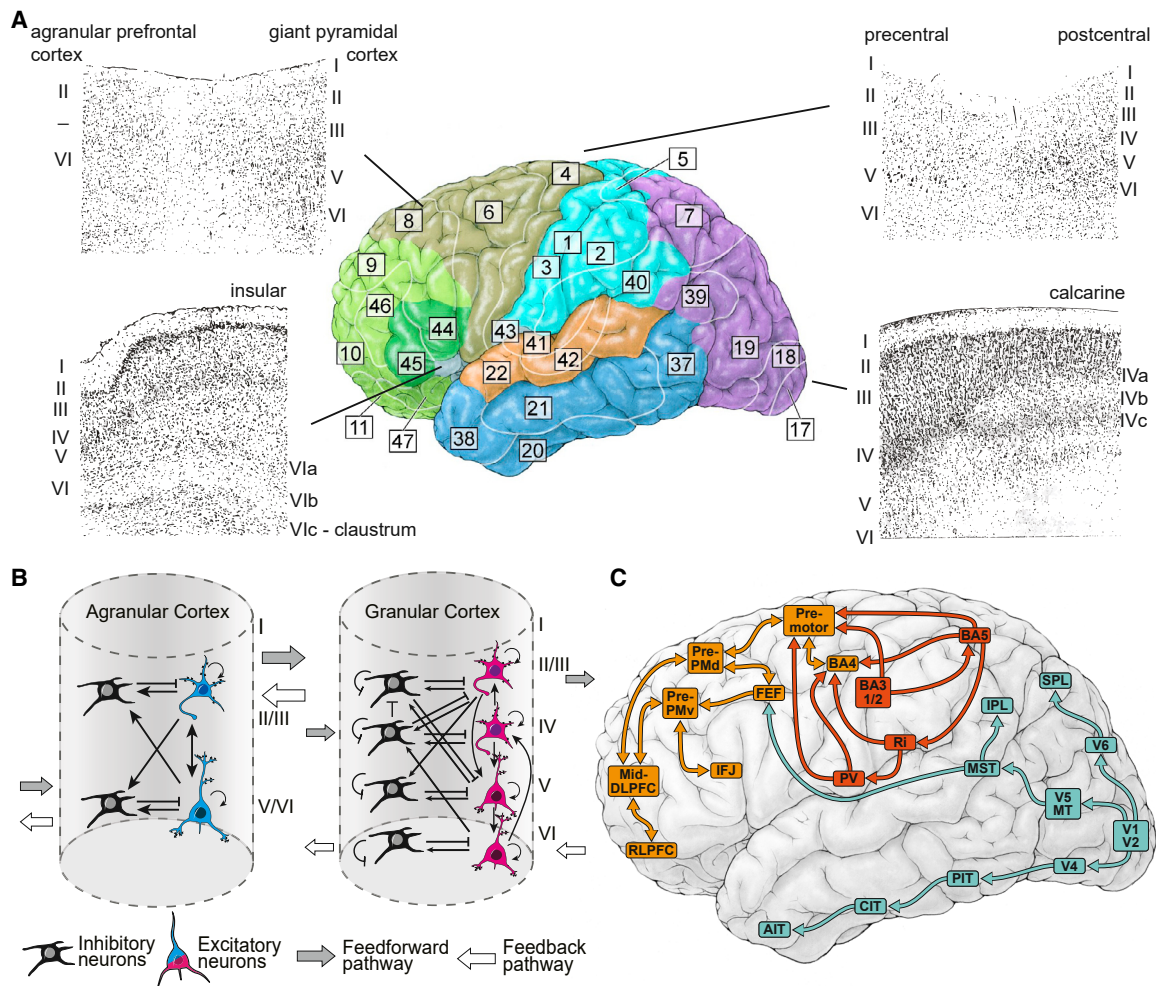


Figure 1. Arealization of the Human Cerebral Cortex

(A) Classical cytoarchitectonic areas described by Brodmann (1909).

(B) Areal differences in local microcircuit architecture between granular and agranular cortices modified from Beul and Hilgetag (2015) and Shipp (2005).

(C) Hierarchical organization between cortical areas, inferred and/or modified from Badre and Nee (2018), Felleman and Van Essen (1991), and Ventre-Dominey (2014).

2017). Even within a single functional area, such as primary motor cortex, the cell and neuron density may vary in a topographic manner, and these differences are thought to reflect changes in the cortical circuitry (Young et al., 2013a).

At the cellular level, systematic studies mapping diversity in the brain have emphasized the remarkable conservation of basic cell types across cortical areas (Harris and Shepherd, 2015). For example, although primary motor cortex has no obvious layer 4 on routine histological sections, excitatory neurons with connectivity profiles typical of L4 neurons have recently been described (Yamawaki et al., 2014), suggesting a conservation of basic cell types and circuit motifs across cortical areas, even with diverse cytoarchitecture and function. Across functional areas, variations in cellular composition are hypothesized to contribute to area-specific variations of microcircuits. Notably, specialized cell types with distinct morphologies and localization include the “Betz” cells in layer V of pri-

mary motor cortex and “von Economo” neurons in layer V of certain areas in the frontal, insular, and anterior cingulate (von Economo and Koskinas, 1925). In rodents, spiny stellate neurons are much more abundant in layer 4 of the primary somatosensory cortex than pyramidal neurons (Egger et al., 1999; Woolsey et al., 1975), and the reverse is true in the visual cortex (Peters and Kara, 1985; Sáez and Friedlander, 2009; Scala et al., 2019). Regional variations in the numbers of many other types of neurons and receptors have been documented throughout the cerebral cortex (Ding et al., 2016; Hendry et al., 1987; Palomero-Gallagher and Zilles, 2019; Schleicher et al., 2000; Xu et al., 2010). Ongoing large-scale efforts that seek to comprehensively characterize the cellular composition and connectivity of cortical areas (Gouwens et al., 2019; Jiang et al., 2015; Markram et al., 2015) have the potential to systematically compare cellular composition and local microcircuitry that may underlie functional variations across cortical areas

and give rise to their higher level hierarchical organization (Figures 1B and 1C).

At the molecular level, initial bulk transcriptomic studies did not reveal major differences in gene expression between cortical areas in adult humans (Khaitovich et al., 2004; Roth et al., 2006; Xu et al., 2018), consistent with the idea that different areas may utilize a conserved set of basic cell types. Nonetheless, limited transcriptional differences were still identified between cortical areas in the adult human brain (Hawrylycz et al., 2012, 2015), including a handful of genes that show abrupt changes in expression at the boundary between the primary and secondary visual cortex (visual cortical areas 17 and 18; Zeng et al., 2012). Because bulk gene expression studies rely on pooling transcripts from millions of cells, cellular composition differences can significantly confound the discovery of cell-type-specific gene expression profiles, particularly for rare cell populations or closely related subtypes (Kelley and Oldham, 2015). To overcome this limitation, single-cell RNA sequencing has recently emerged as a powerful tool for data-driven classification of cell type homology across anatomical areas and species (Aevermann et al., 2018; Hodge et al., 2018). Using this approach, two recent studies in the adult mouse have compared neurons across anatomical regions of the cerebral cortex and revealed that molecularly defined excitatory neuron subtypes segregate according to the area from which they were sampled, and interneuron subtypes were shared across areas (Saunders et al., 2018; Tasic et al., 2018). Although this level of coverage has not yet been achieved in the adult human, initial characterization using *in situ* hybridization (Zeng et al., 2012) and single-nucleus RNA sequencing (Hodge et al., 2018; Lake et al., 2018) indicates that differences in gene expression may also define area- or region-specific subtypes of excitatory neurons in the human cerebral cortex.

The presence of transcriptomically distinct cell types in different cortical areas may impact area-specific computations at multiple levels, including the input-output function of individual neurons (London and Häusser, 2005) and the formation of local and long-distance connections (Averbeck et al., 2009; Harris and Shepherd, 2015; Markov et al., 2013). Testing these predictions will require further validation using emerging technologies to relate molecular cell types to classical definitions based on morphology and physiology. Techniques, such as Patch-seq, now enable combined recovery of morphology, physiology, and gene expression in the same cells (Cadwell et al., 2016; Fuzik et al., 2016; Scala et al., 2019) and will facilitate generation of a more complete inventory of cell types in the brain. In addition, profiling of epigenetic states at single-cell resolution provides an additional molecular perspective on cell type classification (Gray et al., 2017; Luo et al., 2017) and may facilitate the generation of novel tools for visualizing, targeting, and replacing cell types in the brain (Graybuck et al., 2019; Hrvatin et al., 2019; Mich et al., 2019).

Overview of Cortical Development

The cytoarchitectonic and molecular features that distinguish cortical areas discussed above represent only a few examples sampled from a vast body of work. Despite the multitude of well-characterized differences between cortical areas in the

adult brain, many of these differences are not apparent during development. The central question of how cortical areas form during development has been the subject of studies that span several decades. In this review, we focus on discussing early developmental events that establish broad distinctions among the major cortical regions. Two hypotheses have been postulated to explain how the apparently uniform processes of proliferation and differentiation during development give rise to the area-specific variations of the adult cortex. First, the “protomap” hypothesis theorizes that progenitors are pre-patterned to give rise to region-specific neurons with distinct molecular, physiological, and connectivity features (Bishop et al., 2000; Rakic, 1988; Rubenstein and Rakic, 1999). Second, the “protocortex” hypothesis suggests that the cortex is initially homogeneous and develops area-specific features only in response to extrinsic signals, most notably thalamic input (Van der Loos and Woolsey, 1973; Creutzfeldt, 1977; O’Leary, 1989). In the following sections, we will discuss the evidence behind both theories and highlight how novel molecular techniques are beginning to shed light on these long-standing questions.

Progenitors of the Cerebral Cortex

Before the onset of neurogenesis, the neuroepithelium is composed of neuroepithelial stem cells (NESCs) that undergo symmetric divisions that expand the neuroepithelial surface area and determine the size of the “founder” population of neurogenic ventricular radial glia (vRG) cells, whose cell bodies are located in the ventricular zone (VZ). Already at these early stages, morphogen gradients, including fibroblast growth factor (FGF) expressed by the anterior neural ridge, Wnt and bone morphogenetic protein (BMP) signaling from the roof plate, and Sfrp1 and transforming growth factor α (TGF- α) from the ventral pallium, induce the expression of patterning transcription factors in the neuroepithelium and vRG cells (Bayatti et al., 2008; Mallamaci and Stoykova, 2006; Rubenstein et al., 1998). These patterning factors subsequently induce the expression of transcription factors that execute region-specific neurodevelopmental programs and control the cell fate of neurons born in different brain regions. In the neocortex, these transcription factors include EMX1, EMX2, PAX6, LHX2, and COUP-TF1 (Figure 2A). Many of these factors are expressed preferentially in the vRG cells, and their loss of function results in changes in the cortical area map, indicating that patterning transcription factors may contribute to the “protomap” formation (O’Leary et al., 2007).

Around post-conception week (pcw) 12 of human development, a distinct anatomical zone called the outer subventricular zone (OSVZ) forms and is populated by proliferative progenitor cells (Rakic and Sidman, 1968a, 1968b; Sidman and Rakic, 1973; Smart et al., 2002), including cells that are derived from vRG and retain neural stem cell potential but adopt a distinct morphology, dynamic cell behavior, and molecular identity (Figure 2B). These cells are called outer radial glia (oRG) (Hansen et al., 2010; Pollen et al., 2015; Thomsen et al., 2016) and are also referred to as basal radial glia (Fietz et al., 2010; Reillo et al., 2011). It is currently unknown whether the same molecular patterning seen across vRG cells is relayed to the oRG cells. Across the cortical neuroepithelium, the abundance of oRG cells varies, with abundant oRG cell populations found underneath

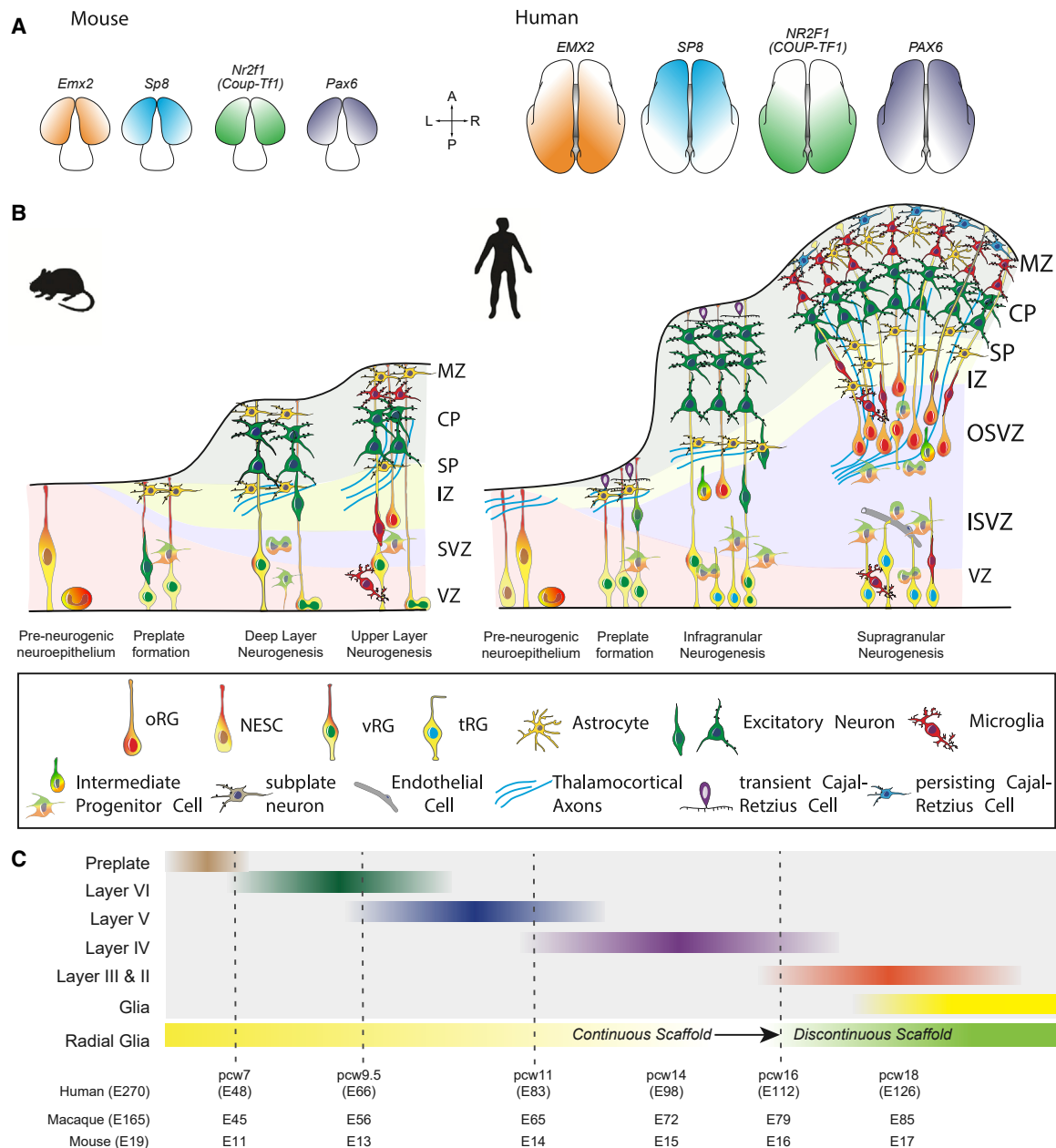


Figure 2. Timing of Neurodevelopmental Events in the Cerebral Cortex

(A) Key patterning centers set up morphogen and transcription factor gradients across the developing neuroepithelium to influence area-specific cell fates. (B) Schematic comparison of the mouse and human cerebral cortical development at peak stages of neurogenesis. Although the processes are broadly conserved, several important differences can be highlighted: prominent expansion of the outer subventricular zone (OSVZ) and of the outer radial glia population that resides therein (Fietz et al., 2010; Hansen et al., 2010; Reillo et al., 2011); expansion of the subplate (SP), which is associated with the expansion of the axonal plexus, but not necessarily cell numbers (Duque et al., 2016); expansion of the upper layer excitatory neuron types (Hodge et al., 2018); discontinuation of the radial glia scaffold (Nowakowski et al., 2016); emergence of persisting Cajal-Retzius cells (Meyer and González-Gómez, 2018); expansion of axonal plexus in the OSVZ and the emergence of multilaminar axonal-cellular compartment (Žunić Isasegi et al., 2018); and early arrival of thalamocortical plexus in the cortical anlage (Marín-Padilla, 1983).

(C) Broad comparison of key neurogenesis periods across species, including data from Clancy et al. (2001) and Rakic (1974). Embryonic days (E) next to species names indicate approximate length of gestation.

the prospective gyri (Nowakowski et al., 2016; Smart et al., 2002), consistent with the hypothesis that basal progenitors may play an important role in gyrification of the cerebral cortex (Kriegstein et al., 2006; Reillo et al., 2011). Control of the cell cy-

cle duration and rate of cell cycle re-entry of oRG cells may play an important role in regulating the tangential extent of individual areas, as well as area-specific cytoarchitectonics and neuronal numbers (Lukaszewicz et al., 2005).

The molecular mechanisms regulating the timing of oRG cell production are unclear but are thought to involve well-established developmental signaling pathways, including LIF and Shh (Martínez-Martínez et al., 2016; Matsumoto et al., 2017; Stahl et al., 2013; Wang et al., 2016; Watanabe et al., 2017). During human supragranular layer production, the vast majority of pia-contacting radial glia fibers originate from cells located in the OSVZ (deAzevedo et al., 2003; Nowakowski et al., 2016; Figure 2B). Neither mouse nor ferret cortical development involves such a dramatic developmental transition of the radial glia scaffold, and in these species, continuous radial glia fiber connections exist between ventricular and pial surfaces of the cortex, even at the end of neurogenesis (Reillo et al., 2011). In the developing ferret, generation of oRG cells is confined to a narrow time window during deep layer neurogenesis (Martínez-Martínez et al., 2016) and involves asymmetric division of vRG cells with one (basal) daughter cell inheriting the pia-contacting fiber (LaMonica et al., 2013). The daughter cell that remains in contact with the ventricle begins to regrow the basal fiber but does not reach the pial surface and is unable to support radial migration to the cortical plate (LaMonica et al., 2013; Nowakowski et al., 2016). These “truncated” radial glia cells emerge sharply around pcw 14–14.5 in humans and acquire a distinct molecular and morphological phenotype (Nowakowski et al., 2016; Rakic, 1978).

The absolute increase in surface area and number of cortical neurons combined with the selective expansion of frontal and parieto-temporal cortical regions is thought to underlie the emergence of advanced cognitive abilities in humans, including perception, language, and reasoning (Geschwind and Rakic, 2013). Because of the central role of radial glia fibers in supporting neuronal migration to the cortical plate (Rakic, 1972), the total number of pia-contacting radial fibers directly predicts the total cortical surface area (Rakic, 1988). Expansive divisions of vRG and NESCs could serve as a fundamental mechanism for regulating the size of any given cortical area (Rakic, 1988). Consistent with this hypothesis, functional experiments in mice promoting NES and vRG expansion, preventing their elimination, or delaying NES differentiation into vRG cells have been shown to result in an expansion of the tangential surface area of the cortical neuroepithelium (Beattie et al., 2017; Chenn and Walsh, 2002, 2003; Haydar et al., 1999; Kuida et al., 1996; Li et al., 2017; Sahara and O’Leary, 2009). In addition, programmed cell death as a mechanism regulating cortical surface area may be underappreciated, although reports of the extent of cell elimination during normal cortical development vary depending on analysis method (Kuida et al., 1996; Rakic and Zecevic, 2000; Wilkie et al., 2004). To what extent these pathways converge and interplay with classical mechanisms of organ size control remains largely unclear (Kunche et al., 2016; Tumaneng et al., 2012). Whether oRG cells directly contribute to the tangential expansion of the cortical surface area also remains unclear, but experiments inducing overproduction or proliferation of OSVZ progenitors in ferrets have suggested a role for this cell type in regulating cortical surface area in mammals (Matsumoto et al., 2017; Nonaka-Kinoshita et al., 2013). Given that the majority of oRG cells are generated at later stages of development than vRG cells, expansive divisions of the oRG cell population would be predicted to

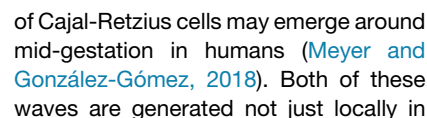
disproportionately expand the surface area and the number of neurons in the upper layers of the cortex relative to deep layers, but evidence for such expansion is currently limited (Borrell, 2018; Nowakowski et al., 2016; Richman et al., 1975; Stahl et al., 2013; Wang et al., 2016). Further studies into the mechanisms of cortical area expansion could advance our understanding of selective expansion of specific cortical areas in humans compared to nonhuman primates.

During peak excitatory neurogenesis, two distinct modes of neuronal production have been described. The direct neurogenesis pathway involves neuronal differentiation directly from asymmetric division of vRG cells and is believed to be more prevalent at early stages of cortical development, at least in mice (Miyata et al., 2001; Noctor et al., 2001). The second mode of neuronal differentiation involves an intermediate progenitor cell (IPC) that divides in the subventricular zone (SVZ). IPCs may re-enter the cell cycle to divide, usually symmetrically, and produce postmitotic neurons (Haubensak et al., 2004; Noctor et al., 2004; Figure 3). In contrast to radial glia, IPCs do not maintain continuous connections with the pial or ventricular surfaces and undergo a stationary division. They also tend to adopt a multipolar morphology, although recent studies suggest that IPCs may also adopt unipolar or bipolar morphologies in primates (Betizeau et al., 2013; Kriegstein and Noctor, 2004; Pollen et al., 2015).

The role of intermediate progenitors in the cortex remains an area of active research, but recent studies suggest that this cell type may play an important role in cell fate decisions in the developing cortex. For example, the IPC population may be more heterogeneous than previously appreciated, and some IPCs generated early in development may be maintained in a quiescent state until upper layer neurogenesis (Mihalas et al., 2016). IPCs are believed to play a critical role in regulating the number of excitatory neurons in the cerebral cortex through transit amplification of the neuronal output from radial glia (Pontious et al., 2008) and may contribute to variations in cortical thickness across areas (Pontious et al., 2008), suggesting that they too may have an essential role in determining cortical area-specific neuronal composition. Consistent with these findings, there are areal differences in the fraction of neurons that are derived from IPCs, particularly in layers 4 and 5 (Vasistha et al., 2015). Other roles have also been attributed to this cell type, including promoting tangential migration of interneurons to the cortex (Sessa et al., 2010) and contributing to the maintenance of vRGs (Yoon et al., 2008). Interestingly, human IPCs located in the OSVZ (Smart et al., 2002) appear to have a substantially increased proliferative capacity, are able to undergo multiple rounds of expansive division (Hansen et al., 2010; Kriegstein et al., 2006), and are hypothesized to adopt diverse morphologies and possibly also differentiate into radial glia (Betizeau et al., 2013). Many interesting questions remain, such as whether IPCs in different cortical areas show distinct molecular properties or fate potential, and, if so, how area-specific identities are passed from radial glia to IPCs.

Differentiation and Maturation of Excitatory Neurons

The developmental time window of neurogenesis varies widely across species. In mice, neurons are generated between embryonic days 11 and 17 (Caviness et al., 1995), whereas in the



different layers and projection classes (Harris and Shepherd, 2015; Lodato and Arlotta, 2015; Molyneaux et al., 2007). In the adult human, layer-specific dissections of the cortex followed by single-nucleus sequencing have identified human-specific markers of cortical layers in the medial temporal gyrus (Hodge et al., 2018), as well as new and previously described markers of layer identity (Zeng et al., 2012). Interestingly, most molecularly defined cell types in the adult human cortex appear to be present in more than one layer, suggesting that a combination of molecular identity and layer position may interact to generate a wide range of cell types both within and across cortical areas.

Mechanisms regulating the decision of cortical neurons to adopt a particular laminar fate remain unclear. A bulk RNA sequencing study spanning prenatal to young adult time periods in macaques found that a number of genes are differentially expressed between prefrontal cortex and occipital cortex and that markers of layer identity emerge between E80 and E90 and are fully defined by birth (Bakken et al., 2016). In both macaque and human, birthdates of excitatory neurons roughly correlate with upper versus deep layer neuronal identity, but distinctions within these groups are not refined until much later (Bakken et al., 2016; Miller et al., 2014). By contrast, in the mouse, a number of birth-dating experiments have shown laminar identity is more precisely determined by neuronal birth date (Greig et al., 2013; Telley et al., 2016).

Development of Inhibitory Cortical Interneurons

Cortical inhibitory interneurons are extraordinarily diverse in terms of their morphology and physiology, and their numbers have increased relative to excitatory neurons over the course of evolution (Defelipe, 2011) along with the appearance of unique interneuron subtypes in humans (Boldog et al., 2018; DeFelipe et al., 2002). Cortical interneurons are generated in the medial and caudal ganglionic eminences, as well as the preoptic area, and migrate tangentially to integrate into local cortical circuits (Faux et al., 2012; Harwell et al., 2015; Mayer et al., 2015). Although some studies suggest that clonally related interneurons are not randomly distributed in the cortex (Brown et al., 2011; Sultan et al., 2016), it is unclear whether this is functionally relevant given the wide spatial distribution (1,500 μ m average intersoma distance) of clonally related interneurons, which also cross functional boundaries (Mayer et al., 2016; Turrero Garcia et al., 2016). Although in most species interneuron migration occurs embryonically, recent studies in the human cortex suggest an extended period of interneuron production that continues through 7 months after birth, at least in the frontal lobe (Paredes et al., 2016). Parvalbumin-positive (PV+) interneurons form dense connections with excitatory neurons, leading to the postulation of a “blanket inhibition” hypothesis (Beutler and Kuhl, 1986; Fino and Yuste, 2011; Packer and Yuste, 2011). Yet neighboring PV+ interneurons are differentially recruited into neuronal ensembles and are thought to participate in complex cognitive computations (Lagler et al., 2016). A recent study in mice has shown that certain circuits between inhibitory interneurons and excitatory neurons form transiently during development and may contribute to normal formation of mature local and thalamocortical microcircuits (Marques-Smith et al., 2016).

Several studies have shed light on the developmental mechanisms guiding interneuron migration and wiring. Analysis of the

Fezf2 mutant mouse, in which deep-layer subcortical excitatory projection neurons are missing, shows a mislamination of deep-layer interneurons although upper-layer interneurons remain unaffected (Lodato et al., 2011). In a complementary study, the *Satb2* knockout model, in which callosal projection neurons are misspecified, shows a specific mislamination of upper-layer interneurons, although deep-layer interneurons are unaffected (Wester et al., 2019). In addition, induction of specific types of cortical excitatory neurons in an ectopic, subcortical location results in recruitment of interneurons of the correct cortical layer identity (Lodato et al., 2011), suggesting that extrinsic cues from excitatory neurons, not birthdate, is a key determinant of appropriate layer-specific interneuron migration and positioning. In addition to the precise cell-type-specific wiring diagram described among different morphologically distinct subtypes of interneurons (Jiang et al., 2015), recent studies also suggest that interneurons form synaptic connections with different subtypes of excitatory neurons in a cell-type-specific manner. For example, parvalbumin-positive interneurons in layer 5 of the prefrontal cortex preferentially inhibit corticofugal projection neurons over neighboring callosal neurons (Lee et al., 2014). Similarly, in the medial entorhinal cortex, parvalbumin-positive and cannabinoid-type-1-receptor-positive interneurons in layer 2 preferentially synapse onto calbindin-positive callosal projection neurons while avoiding neighboring reelin-positive projection neurons that project to the dentate gyrus (Varga et al., 2010; Armstrong et al., 2016). Fate conversion experiments in which postmitotic layer 2/3 callosal projection neurons are reprogrammed to subcortically projecting neurons recruit perisomatic input from parvalbumin-positive interneurons to levels similar to that of endogenous subcortically projecting neurons found in layer 5 despite their ectopic location in layer 2/3 (Ye et al., 2015). These findings suggest that the identity of projection neurons, at least in part, dictates the establishment of appropriate inhibitory synapses in a class-specific manner.

Interneurons have been proposed to control the rate of maturation of cortical circuits and plasticity. One recent study has suggested a role for inhibitory interneurons in activity-dependent plasticity in adult mice (Adler et al., 2019). Heterochronic transplantation experiments in which embryonic interneurons are transplanted into juvenile and adult cortex have shown that interneurons, and particularly MGE-derived interneurons, can reopen ocular dominance plasticity well beyond the critical period (Davis et al., 2015; Southwell et al., 2010). However, the opposite experiment of transplanting mature interneurons to an embryonic circuit to determine whether it can precipitate faster than normal maturation has not yet been performed, and it remains unclear whether interneurons act as bidirectional master regulators of ocular dominance plasticity.

Interneurons are disproportionately affected by apoptosis compared to excitatory neurons, with an estimated loss of ~30% of interneurons during early postnatal development compared to ~12% of excitatory neurons (Wong et al., 2018). This process is regulated at least in part by activity-dependent mechanisms (Priya et al., 2018). Interestingly, deep-layer interneurons die earlier than interneurons of the upper layers, and waves of interneuron apoptosis are preceded by projection neuron apoptosis, suggesting that these two events may be

linked (Wong et al., 2018). Furthermore, projection neuron activity was shown to promote the survival of interneurons via negative regulation of PTEN (Wong et al., 2018). These findings suggest that one mechanism by which excitatory neurons orchestrate the assembly of region-specific cellular components could be via regulation of inhibitory interneuron survival.

Molecular Correlates of Areal Identity

Molecular signatures of positional identity are apparent from an early developmental stage. In the embryonic and early postnatal mouse, a number of genes show differential expression across cortical regions (Bishop et al., 2000). For example, although *Cad8* is broadly expressed across the entire cortex within layer 5, it is also highly expressed in layer 2/3 in rostral cortical areas (Nakagawa et al., 1999; Suzuki et al., 1997). *Cad6* expression is enriched in the dorsal and lateral developing isocortex, corresponding to the prospective somatosensory and auditory areas, but is lowly expressed, especially in layers 4 and 5, in the extreme rostral isocortex (Nakagawa et al., 1999; Suzuki et al., 1997). *RORB* (formerly known as RZR-beta) and *p75* (also known as *NGFR*) show opposing graded expression patterns across the isocortex, with *RORB* mRNA expressed in regions rostral to the developing visual cortex, and *p75* expression is found only in the subplate of caudal regions (Mackarechtschian et al., 1999; Rubenstein et al., 1999). *EPHA7* is expressed throughout most of the developing isocortex but at much lower levels in intermediate regions corresponding to the somatosensory area (Rubenstein et al., 1999). Finally, *EFNA5* is expressed most highly in the dorsolateral isocortex corresponding to the somatosensory area (Mackarechtschian et al., 1999). These are just a few of the many examples of area-specific gene expression patterns, and the major findings from these and other studies are summarized in Table 1.

The first systematic characterization of areas in human development was performed using exon arrays to explore a number of rostral, temporal, and occipital cortical regions as well as subcortical brain regions during mid-gestation (Johnson et al., 2009). Hundreds of genes were found to be differentially expressed between rostral and caudal brain regions, and samples from motor and somatosensory cortices showed an intermediate expression profile, consistent with the idea that a gradient of morphogen and gene expression patterns may give rise to frontal, central, and occipital cortical areas (O'Leary et al., 2007). Additionally, distinct transcriptional programs were observed within regions of the developing prefrontal cortex, most notably in the orbital prefrontal cortex (Johnson et al., 2009), indicating that transcriptional mechanisms may also be engaged for intra-areal refinement. Overall, examination of cortical areas during development has shown that the majority of expressed genes in the human brain are differentially expressed across brain regions or time, but these differences universally diminish over the course of development (Kang et al., 2011). Similar trends were observed in the macaque, with the most dynamic changes occurring early in postnatal development (Bakken et al., 2015). A pair of recent studies that surveyed 16 brain regions transcriptomically across developmental time in the human and macaque found

a "cup-shaped pattern" of development, with large regional differences early in development narrowing and re-emerging during childhood, at which point these transcriptional changes were paired with epigenetic restructuring (Li et al., 2018; Zhu et al., 2018). Interestingly, bulk tissue studies have revealed only limited transcriptional distinctions between cortical areas in the adult human brain, as discussed earlier (Hawrylycz et al., 2012, 2015; Khaitovich et al., 2004; Roth et al., 2006; Silbereis et al., 2016).

Single-cell sequencing approaches are providing new insights into the processes of early cortical arealization. For example, single-cell RNA sequencing has identified hundreds of differentially expressed genes between cells of the same broad class between developing prefrontal (PFC) and primary visual (V1) cortical areas (Nowakowski et al., 2017). Although positional differences in gene expression were apparent at all stages of lineage progression (radial glia, intermediate progenitors, and postmitotic neurons), they became amplified over the course of neuronal differentiation, with only a few transcription factors differentially expressed at the level of radial glia and hundreds of transcripts distinguishing postmitotic neurons. In addition to previously identified markers for developing PFC and V1, novel candidates restricted to specific subtypes of cells in PFC or V1 were identified using this single-cell approach, including *CPNE8* in the upper layers of PFC and *HCRT2* in subplate neurons of V1. These transcriptomic signatures of positional identity precede those of laminar specification (Nowakowski et al., 2017), suggesting that molecular correlates of laminar identity emerge later in development. Furthermore, there appeared to be a narrow transition zone between rostral and caudal gene expression patterns, suggesting that rostral and caudal lineages give rise to discrete cell types rather than representing opposite ends of a developmental gradient. The early divergence of area-specific excitatory neurons is consistent with a protomap hypothesis in which multiple excitatory neuron lineages emerge simultaneously across the developing cortex. It is possible that a limited set of transcription factors differentially expressed in radial glia initiate divergent intrinsic gene regulatory programs, which are later amplified in an area-specific manner upon differentiation.

The ability to query chromatin state at the single-cell level is a new frontier that expands our ability to identify epigenetic variations across cell types and brain regions (Graybuck et al., 2019; Hrvatin et al., 2019; Mich et al., 2019). Recent work in the adult human shows a strong association between chromatin state and brain region (Lake et al., 2018). In addition, chromatin state strongly correlates with cell type identity (Luo et al., 2017), suggesting that analysis of chromatin or epigenetic states of individual cell types could further elucidate the regulatory processes underlying cell fate specification (Gray et al., 2017). Along these lines, a recent single-cell transcriptomic study in developing mouse showed that the temporal progression of apical progenitor states is epigenetically regulated by the Polycomb repressor complex PRC2 (Telley et al., 2019). Extending these studies across developmental time points and brain regions in humans will further illuminate the extent to which a protomap might be encoded in progenitor cells.

Table 1. Area-Enriched Genes and Knockout Phenotypes

Gene	Organism	Expression Pattern	Mouse Knockout Cortical Phenotype	Relevant References
<i>AUTS2</i>	human; mouse	frontal cortex	neonatal lethal in mouse; defects in neuronal migration, axonal elongation, and neuritogenesis in mouse embryos.	Bedogni et al., 2010a, 2010b; Hori et al., 2014; Srinivasan et al., 2012
<i>BCL6</i>	mouse	somatosensory cortex at birth; rostral in adulthood.	unknown	Leamey et al., 2008
<i>BHLHB5</i>	mouse	postmitotic neurons of primary sensory areas (visual, somatosensory, and auditory cortex) layers II–V	aberrant gene expression and structural organization of somatosensory and caudal motor cortices	Joshi et al., 2008
<i>BLN2</i>	human	high rostro-caudal gradient	unknown	Lambert et al., 2011
<i>C13ORF38</i>	human	high expression in temporal lobe	unknown	Pletikos et al., 2014
<i>CBLN2</i>	human; mouse	high-to-low rostro-caudal gradient	unknown	Johnson et al., 2009; Miura et al., 2006
<i>CDH6</i>	mouse	high-to-low caudal-rostral gradient in postmitotic neurons	unknown	Terakawa et al., 2013
<i>CDH8</i>	ferret; human; macaque; mouse	frontal cortex	autism-like behavior; reduced neuronal complexity	Bernier et al., 2014; Friedman et al., 2015; de Juan Romero et al., 2015
<i>CLMP</i>	human	high-to-low rostro-caudal in human; no areal differences in macaque	unknown	Pletikos et al., 2014
<i>CNTN4</i>	human	high rostro-caudal gradient	unknown	Lambert et al., 2011
<i>CNTNAP2</i>	human	high-to-low rostro-caudal gradient	reduced spine density and levels of GluA1 of AMPA receptors in spines	Johnson et al., 2009; Lambert et al., 2011; Varea et al., 2015
<i>CPNE8</i>	human	frontal cortex, upper layer excitatory neurons	unknown	Lambert et al., 2011; Nowakowski et al., 2017
<i>CRYM</i>	mouse	high-to-low caudal-rostral gradient	unknown	Bedogni et al., 2010b; Leamey et al., 2008
<i>CUX1</i>	mouse	higher in somatosensory than in motor cortex in layers 2–4	aberrant dendritic morphology of upper-layers projection neurons	Cubelos et al., 2015; Nieto et al., 2004
<i>DIAP3</i>	mouse	subcerebral projection neurons of the motor cortex	unknown	Arlotta et al., 2005
<i>DKK3</i>	mouse	visual cortex	no obvious phenotype in cortex	Barrantes et al., 2006; Leamey et al., 2008
<i>DUSP6</i>	mouse	somatosensory cortex	unknown	Leamey et al., 2008
<i>EOMES</i>	ferret; human	high-to-low caudal-rostral gradient; no gradient is observed in mouse	microcephaly and behavioral defects; reduction of upper layer projection neurons	Arnold et al., 2008; de Juan Romero et al., 2015; Nowakowski et al., 2017
<i>EPHA3</i>	macaque	high-to-low caudal-rostral gradient in macaque subventricular and intermediate zones	no obvious phenotype	Donoghue and Rakic, 1999; Vaidya et al., 2003
<i>EPHA5</i>	mouse	somatosensory cortex	formation of abnormal cell aggregates and abnormal spine morphology	Cooper et al., 2009; Das et al., 2016
<i>EPHA6</i>	mouse; macaque	cortical plate of developing occipital cortex	formation of abnormal cell aggregates and abnormal spine morphology	Bedogni et al., 2010b; Das et al., 2016; Donoghue and Rakic, 1999
<i>EPHA7</i>	macaque; mouse	high-to-low rostro-caudal in mouse; caudal-rostral gradient in macaque early development (E65)	dendrites are longer and more complex	Clifford et al., 2014; Donoghue and Rakic, 1999

(Continued on next page)

Table 1. Continued

Gene	Organism	Expression Pattern	Mouse Knockout Cortical Phenotype	Relevant References
EMX2	human; mouse	high-to-low medial-lateral gradient	reduction of caudal-medial identity	Gulisano et al., 1996; Ip et al., 2010; Mallamaci and Stoykova, 2006
FGF17	mouse	frontal cortex	reduction of dorsal frontal cortex; rostral shift in cortical sensory areas	Cholfin and Rubenstein, 2007
FGFR2	ferret; mouse	high-to-low caudal-rostral gradient in mouse ventricular zone and ferret outer subventricular zone	reduction of projection neurons in medial prefrontal cortex observed in conditional knockout in radial glia cells	de Juan Romero et al., 2015; Stevens et al., 2010
FGFR3	ferret; human; mouse	high-to-low caudal-rostral gradient	reduction of cortical volume	de Juan Romero et al., 2015; Moldrich et al., 2011; Nowakowski et al., 2017
FLRT3	mouse	visual cortex	altered distribution of projection neurons during development	Leamey et al., 2008; Seiradake et al., 2014
HCRTR2	human	frontal cortex, deep-layer excitatory neurons	unknown	Nowakowski et al., 2017
ID2	mouse	in intermediate and caudal cortex is expressed in layer 5; in frontal cortex is expressed in layer 2/3	unknown	Bulfone et al., 1995
IGFBP4	mouse	subcerebral projection neurons of the motor cortex	unknown	Arlotta et al., 2005
IGSF4A	mouse	visual cortex	unknown	Leamey et al., 2008
KBTBD9	mouse	somatosensory cortex	unknown	Leamey et al., 2008
LHX2	ferret; mouse	high-to-low caudomedial-rostral gradient during development	barrel cores and barrel walls in somatosensory cortex fail to form	Chou et al., 2009; de Juan Romero et al., 2015; Shetty et al., 2013
LIX1	mouse	subcerebral projection neurons of the visual cortex	unknown	Moeller et al., 2002
LMO3	mouse	parietal cortex	behavioral defects	Bulchand et al., 2003; Savarese et al., 2014
LMO4	human; mouse	postmitotic neurons of motor cortex and higher order sensory areas	disrupted molecular identity and connectivity of rostral motor cortex	Cederquist et al., 2013; Lambert et al., 2011
LUZP2	mouse	somatosensory cortex	unknown	Leamey et al., 2008
NHLH1	mouse	high-to-low caudal-rostral gradient	no obvious phenotype	Elsen et al., 2013; Krüger and Braun, 2002
NPN2	mouse	high-to-low caudal-rostral gradient	subcerebral neurons of the visual cortex fail to prune their axons	Low et al., 2008
NPY	human	high-to-low caudal-rostral gradient; no specificity in mouse	unknown	Johnson et al., 2009
NR1F2	ferret; mouse; rat	high-to-low rostro caudal gradient	unknown	Miyashita-Lin et al., 1999; Rowell et al., 2010; Schaeren-Wiemers et al., 1997
NR2F1	human; mouse	high-to-low caudal-rostral gradient in cortical progenitors and postmitotic neurons	expansion of motor cortex at expense of sensory areas	Armentano et al., 2006; Nowakowski et al., 2017
NR2F2	human; macaque	high expression in temporal lobe	unknown	Pletikos et al., 2014
NR4A2	human	parieto-temporal cortex	unknown	Lambert et al., 2011
ODZ1	mouse	high-to-low rostro caudal gradient in layer 4 and subplate neurons	unknown	Li et al., 2006
ODZ2	human; mouse	layer 5 neurons of visual cortex	binocular circuits fail to form	Leamey et al., 2008; Li et al., 2006; Nowakowski et al., 2017; Young et al., 2013b

(Continued on next page)

Table 1. Continued

Gene	Organism	Expression Pattern	Mouse Knockout Cortical Phenotype	Relevant References
<i>ODZ3</i>	mouse	deep-layer neurons of the visual cortex	formation of eye dominance domains in the visual cortex	Leamey et al., 2008 ; Li et al., 2006 ; Merlin et al., 2013
<i>ODZ4</i>	mouse	high-to-low caudal-rostral gradient	hypomyelination of the CNS	Leamey et al., 2008 ; Li et al., 2006 ; Suzuki et al., 2012
<i>P75</i>	rat; mouse	high-to-low caudal-rostral gradient	increased excitability of neurons; enhanced cholinergic innervation into visual cortex	VON Bohlen und Halbach and VON Bohlen und Halbach, 2016 ; Gibon et al., 2015 ; Mackarechtschian et al., 1999 ; Mallamaci et al., 2000
<i>PAX6</i>	mouse	high-to-low rostro-caudal latero-medial gradient	perinatal lethal; conditional mutant has a dramatic decrease of upper-layer neurons, increase of deep-layer neurons reaching the marginal zone, and increased number of oligodendrocytes; phenotype is particularly pronounced in frontal cortex	Stoykova et al., 2000 ; Tuoc et al., 2009
<i>PCDH8</i>	mouse	high-to-low caudal-rostral gradient; no specificity in mouse	no obvious phenotype	Bedogni et al., 2010b ; Yamamoto et al., 2000
<i>PENK</i>	human	high rostro-caudal gradient	unknown	Lambert et al., 2011
<i>PLXA3</i>	mouse	high-to-low caudal-rostral gradient early postnatally	no obvious defect; however, in double knockout with <i>Plxa4</i> , the pruning phenotype of <i>Plxa4</i> is increased	Low et al., 2008
<i>PLXA4</i>	mouse	high-to-low caudal-rostral gradient early postnatally	subcerebral neurons of the visual cortex fail to prune their axons	Low et al., 2008
<i>PLXND1</i>	macaque; mouse	high-to-low caudal-rostral gradient in postmitotic neurons	hem-derived Cajal-Retzius cells reach more dorsal neocortical regions	Bribián et al., 2014 ; Watakabe et al., 2006
<i>SATB2</i>	human	high-to-low rostro-caudal, co-expressing with <i>BCL11B</i> in deep layers until sharp boundary segregates expression with <i>SATB2</i> in upper layers	upper layer callosal projection neurons fail to form	Alcamo et al., 2008 ; Britanova et al., 2008 ; Nowakowski et al., 2017
<i>SEMA3E</i>	mouse; macaque	high-to-low caudal-rostral gradient in postmitotic neurons	hem-derived Cajal-Retzius cells reach more dorsal neocortical regions	Bribián et al., 2014 ; Watakabe et al., 2006
<i>SLN</i>	human	high rostro-caudal gradient	unknown	Lambert et al., 2011
<i>SOX9</i>	human	parieto-temporal cortex	unknown	Lambert et al., 2011
<i>SP8</i>	mouse	high-to-low anterior-medial to posterior-lateral gradient in cortical progenitors	unknown	Sahara et al., 2007
<i>TBR1</i>	mouse	high-to-low rostro-caudal	expression of caudal genes in frontal cortex	Bedogni et al., 2010b
<i>THBS1</i>	human	high rostro-caudal gradient	unknown	Lambert et al., 2011
<i>TSHZ2</i>	mouse	occipital cortex	unknown	Bedogni et al., 2010b
<i>USP6</i>	mouse	somatosensory cortex	unknown	Leamey et al., 2008
<i>VSTM2L</i>	human	high rostro-caudal gradient	unknown	Lambert et al., 2011
<i>WNT7B</i>	human; macaque	high-to-low caudal-rostral gradient in postmitotic neurons	unknown	Ozair et al., 2018 ; Pletikos et al., 2014
<i>WSCD1</i>	mouse	high-to-low rostro-caudal in layer 6 neurons and subplate	unknown	Bedogni et al., 2010b

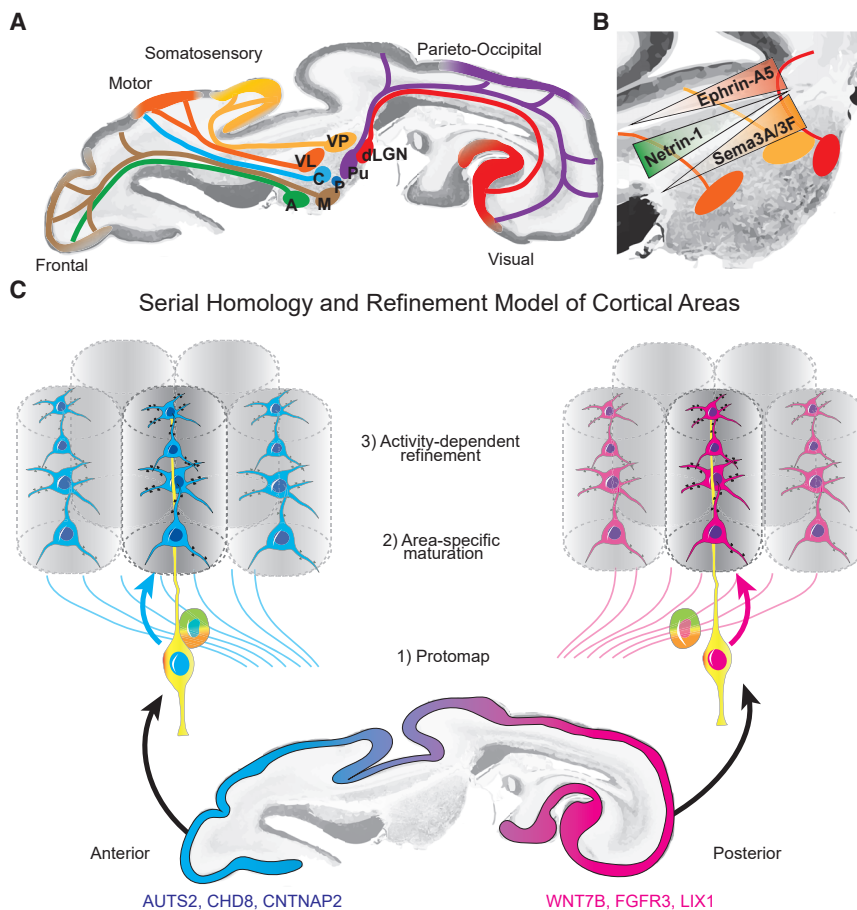


Figure 4. Mechanisms of Arealization

(A) Early development of thalamocortical tracts provides anatomical basis for modality-specific responses in the cortex, activity-dependent changes in cortical area size, and functional circuit development.

(B) Morphogen gradients contribute to shaping thalamic areal specification.

(C) Serial homology and refinement model, in which area-specific gene expression programs establish an initial “protomap,” which is further refined by area-specific maturation signals and activity-dependent processes to generate the final mature cortical areas.

jections around E12, and the first thalamocortical axons reach the cortical subplate around E14, where they pause for several days before invading the cortical plate to synapse in layer 4. Axons originating from different thalamic nuclei retain their topographic mapping by differentially responding to axon guidance cues, especially as they traverse the striatum, and segregate to their appropriate target cortical area (Molnár and Blakemore, 1995; Molnár et al., 1998; Bielle et al., 2011a, 2011b; Shimogori and Grove, 2005; Figures 4A and 4B). Upon arrival at the cortical primordium, thalamocortical axons have been shown to form transient synapses with subplate cells (Molliver et al., 1973), although the exact role of these connections is unknown. Interestingly, studies

Extrinsic Mechanisms of Cortical Arealization

In addition to early patterning of the cortical neuroepithelium (i.e., protomap) and intrinsic genetic mechanisms regulating neurogenesis, postmitotic factors, such as signaling molecules expressed by the subplate or released by the thalamocortical axons, may further refine the gene regulatory networks that give rise to individual cell types and circuits (Barber et al., 2015; Callaway and Borrell, 2011; Ghosh et al., 1990; Kraushar et al., 2015; Ozair et al., 2018; Pouchelon et al., 2014). One such example is signaling via Cajal-Retzius cells, which may also contribute to cortical arealization by adopting a subtype-specific distribution that influences the identity of local excitatory neurons postmitotically (Barber et al., 2015; Borello and Pierani, 2010). A large body of work indicates a substantial role for thalamic input in promoting cortical arealization. Here, we will discuss early events in arealization and refer readers to a number of excellent reviews on the role of thalamic inputs in formation of more refined maps during critical periods of postnatal development (Bednar and Wilson, 2016; Feldman and Brecht, 2005; Inan and Crair, 2007).

The thalamus is a subcortical structure of the diencephalon that receives and modulates sensory input from the periphery, as well as inputs from the cortex, cerebellum, and basal ganglia, and projects predominantly back to the cortex in an area- and modality-specific manner (Haber and Calzavara, 2009; Figure 4A). In the developing mouse, thalamic neurons begin to send out their pro-

jections around E12, and the first thalamocortical axons reach the cortical subplate around E14, where they pause for several days before invading the cortical plate to synapse in layer 4. Axons originating from different thalamic nuclei retain their topographic mapping by differentially responding to axon guidance cues, especially as they traverse the striatum, and segregate to their appropriate target cortical area (Molnár and Blakemore, 1995; Molnár et al., 1998; Bielle et al., 2011a, 2011b; Shimogori and Grove, 2005; Figures 4A and 4B). Upon arrival at the cortical primordium, thalamocortical axons have been shown to form transient synapses with subplate cells (Molliver et al., 1973), although the exact role of these connections is unknown. Interestingly, studies ablating subplate cells have demonstrated a critical role for these cells in the development of normal cortical circuits (Ghosh et al., 1990). During human development, projections from the thalamus are present in the cortical neuroepithelium even before the onset of neurogenesis, suggesting that thalamocortical afferents may play an even more important role in patterning early cortical progenitors (Alzu'bi et al., 2019; Marin-Padilla, 1983). In animal models, two main approaches have been undertaken to investigate the contribution of thalamocortical inputs to areal specification: (1) manipulating the quantitative amount of thalamocortical input while preserving the qualitative type of input or “modality” and (2) rerouting sensory inputs to different thalamic nuclei. These studies have been the subject of recent excellent reviews (Simi and Studer, 2018), and we will discuss here only a handful of notable examples from each of these categories.

Experimentally increasing or decreasing the size of the dorsal lateral geniculate nucleus (dLGN) (the major thalamic nucleus involved in the visual pathway) via genetic manipulation of SHH signaling in mice results in a corresponding change in the size of the primary visual cortex (Vue et al., 2013). Conversely, experimental closure of the eye (“enucleation”) in ferrets during early postnatal development results in reduced proliferation of OSVZ radial glia and a reduction of both dLGN and primary visual cortex size (Reillo et al., 2011). Thalamus and cortex explant co-culture studies have demonstrated that thalamocortical axons express

FGF and are able to regulate radial glia proliferation (Dehay et al., 2001). Given the previously discussed role of the radial glial scaffold in regulating the tangential surface area of cortex, these findings suggest a possible mechanism whereby thalamocortical input selectively regulates the size of cortical areas. In addition, a recent study found that prenatal thalamocortical calcium waves are required for appropriate barrel organization in mouse somatosensory cortex (Antón-Bolaños et al., 2019), further underscoring the role of extrinsic factors in regulating the development of the cerebral cortex.

Enucleation experiments performed in monkey by removal of the retina during prenatal development (before E80) also resulted in a dramatic reduction of the size of the primary visual area (striate cortex; “area 17”) and changes in cortical folding (Dehay et al., 1989; Rakic, 1988), although when performed at later stages of development (after E80), more modest changes in the size of the striate cortex were observed (Dehay et al., 1996a). It has been proposed that depriving dLGN input to the area 17 neurons that would normally receive it would result in the formation of a hybrid “area X” with features intermediate between area 17 and the adjacent extrastriate area 18 (Rakic, 1988, 1991), suggesting a role for both genetically predetermined and area-specific thalamic inputs in development of area 17. However, other studies have found that this region (which they refer to as default extrastriate cortex or DEC instead of area X) is cytoarchitectonically indistinguishable from normal extrastriate area 18 (Dehay et al., 1996b). More recently, molecular tools have enabled targeted silencing of neuronal activity in distinct thalamic nuclei to further probe the role of activity in shaping cortical circuits and arealization. For example, synchronized calcium waves propagating through gap junctions across cells in each of the modality-specific thalamus nuclei are necessary for appropriate specification of cortical area size (Moreno-Juan et al., 2017).

Studies on the role of modality-specific input on cortical development and function have supported the idea that different cortical areas can perform similar fundamental computations. In these experiments, misrouting retinal axons to the main thalamic somatosensory nucleus (Métin and Frost, 1989) or auditory nucleus (Roe et al., 1992; Sur et al., 1988) in newborn animals led to development of orientation selectivity in non-visual areas. Furthermore, rerouting retinal input onto auditory pathways leads to the development of orientation modules and long-range horizontal connectivity patterns reminiscent of those seen in native primary visual cortex (Sharma et al., 2000), suggesting that the pattern of afferent input profoundly alters intracortical connectivity and contributes to cortical area map formation. A recent study showed that, following enucleation in the mouse, cortical layer V neurons aberrantly project to first-order dLGN instead of the expected higher-order superior colliculus (Grant et al., 2016), which raises the possibility that sensory experience is also important for the development of appropriate transthalamic cortico-cortical circuits. Moreover, it appears that manipulations of thalamocortical input can alter the terminal specification of neuronal identity. While interrogating the specification of layer IV neurons in the somatosensory cortex, primary S1 neurons were respecified to molecularly and functionally resemble secondary S2 neurons when their thalamic input nucleus was ablated (Pouchelon et al., 2014). Similarly, ablation

of geniculocortical afferents prevents the development of patterned gene expression that distinguishes higher order visual areas from V1 (Chou et al., 2013). Elimination of all thalamocortical projections does not entirely abolish the development of area-specific gene expression domains (Miyashita-Lin et al., 1999), although the formation of sharp boundaries between cortical areas depends on thalamocortical input (Vue et al., 2013).

Integration of Intrinsic and Extrinsic Inputs

As noted above, projections from the thalamus are present in the cortical neuroepithelium even before the onset of neurogenesis during human development, making it difficult to experimentally tease apart the relative contributions of genetic predisposition of progenitors (i.e., protomap) and thalamocortical inputs (i.e., protocortex) in areal specification. A few studies have investigated the degree of functional interchangeability, or competency, of cells located in different developing brain regions when transplanted to a heterotopic location that receives an alternate source of thalamic input. Cortical transplantation experiments in rodents have shown different results, depending on the embryological age of the donor cortex and specific cortical areas examined. When occipital cortex progenitors are harvested at embryonic day 12 (E12) and grafted into the parietal somatosensory cortical area of newborn hosts, they adopt the pattern of reciprocal thalamic connections and cytoarchitectonic organization of the heterotopic area (Gaillard et al., 2003). Even late embryonic visual cortex (E17 and E18) progenitors transplanted into neonatal somatosensory cortex develop structures resembling barrel fields (Schlaggar and O’Leary, 1991), although the degree of similarity to native somatosensory cortex in terms of connectivity and function was not examined. In contrast, progenitors harvested from the embryonic occipital cortex at E16 and transplanted into neonatal motor cortex have been shown to retain occipital-like connectivity patterns in line with their site of origin (Ebrahimi-Gaillard et al., 1994). Mouse-embryonic-stem-cell-derived neurons transplanted into newborn mouse frontal cortex tend to follow the projection patterns of visual and limbic areas (Gaspard et al., 2008), and cortical injury models in the adult rodent brain have shown that damaged visual circuits, but not motor circuits, can be re-established by transplanting stem-cell-derived excitatory neurons (Falkner et al., 2016; Michelsen et al., 2015). Together, these results suggest that cortical areal identity, at least between motor and sensory areas, is to some degree prespecified during embryonic development and influences the ability of neurons to integrate into functional circuits. However, because of technical challenges associated with these experiments, many questions remain about the efficiency of integration, the role of maturation stage, and regional variation that may affect the efficiency of heterotopic transplantation.

To reconcile the long-standing models of cortical arealization embodied by the protomap and protocortex hypotheses (Van der Loos and Woolsey, 1973; Creutzfeldt, 1977; O’Leary et al., 2007; Shatz, 1992; Woolsey and Van der Loos, 1970), we propose a model of serial homology in which intrinsic and extrinsic factors both contribute to the establishment of area-specific cell types and circuits (Figure 4C). According to this model, intrinsic genetic programs and local secreted factors establish initial

“proto-regions,” and activity-dependent mechanisms lead to progressive refinement and the formation of sharp boundaries between functional areas in the mature isocortex. One implication of this model could be that of developmental constructivism. Genetic pre-programming of proto-regions may be necessary to maintain region-specific regulatory programs underlying neurogenesis throughout evolution. On the other hand, unlike the determinate development of *C. elegans*, where developmental lineage history of each cell can be precisely mapped across individuals, mammalian nervous system development is indeterminate and emerges from many parallel and homologous lineages. One evolutionary advantage of this model is that of size control, because individual neural stem cells can integrate extracellular signals to control the number of cell divisions they undergo and ultimately the number of neurons they produce. However, this developmental pattern poses new challenges, including that of terminal fate selection. By retaining some degree of fate plasticity, the identity of postmitotic neurons can be later refined by activity, offering a solution to the challenges associated with indeterminacy of developmental lineage. Further research is needed into the interaction between gene regulatory networks and extrinsic signals to provide more complete understanding of developmental mechanisms that give rise to the molecular differences between homologous subtypes of excitatory neurons and local cortical circuitry that ultimately supports cortical function.

Development of Cortical Circuits

The emergence of cognitive capabilities necessitates the formation of appropriate synaptic connections and functional networks during development. Despite significant advances in our understanding of the molecular programs that generate diverse neuronal cell types, the developmental programs that shape neural networks and direct synaptic specificity in the developing cerebral cortex remain largely unknown but are thought to involve an array of *trans*-synaptic cell adhesion molecules (Südhof, 2018) as well as synaptic activity (Kwon and Sabatini, 2011; Oh et al., 2016).

In the macaque, the earliest synapses form in the cortex around E50 in the subplate and the marginal zone, and the first synapses in layer IV of the cortical plate emerge around E65 (Bourgeois and Rakic, 1993; Rakic et al., 1986, 1994). Peak synaptic numbers are reached during early postnatal development (approximately 2 months after birth), followed by elimination of the overproduced synapses (Changeux and Danchin, 1976). In the developing human cortex, synapses in the marginal zone are present as early as pcw 5 (Molliver et al., 1973; Zecevic, 1998). Although synaptogenesis may occur very early in human development, mature membrane properties are not seen until pcw 14, and cells capable of firing repetitive action potentials are not seen until around pcw 18 (Moore et al., 2009). This maturation of excitatory neurons coincides with the onset of spontaneous activity at pcw 18 (Moore et al., 2011) but precedes the emergence of the earliest thalamocortical synapses in layer IV of the visual cortex, which occurs around pcw 19 (Hevner, 2000). Although synaptogenesis and pruning in humans follows a similar trajectory across cortical areas, the total synaptic density peaks at around 3 months after birth in sensory areas and at

around 15 months after birth in prefrontal areas (Huttenlocher and Dabholkar, 1997). The specificity and permanence of these early connections formed among excitatory neurons during development are not well understood.

Connectivity across the prospective areas also emerges early in development and has been most extensively studied in the context of the development of cat visual cortex (Callaway and Katz, 1990, 1991, 1992; Dehay et al., 1984, 1988a; Innocenti and Clarke, 1984; Innocenti et al., 1988; Katz and Callaway, 1992; Price and Blakemore, 1985a). Injections of neuronal tracers revealed many more projections during development than in adult stages, suggesting an initial overproduction of cortico-cortical connections, followed by selective loss of specific connections (Price and Blakemore, 1985a, 1985b). However, studies in macaque have not revealed similar trends (Barone et al., 1995, 1996; Dehay et al., 1988b), suggesting that, in primates, lasting cortico-cortical connections may develop without forming transient exuberant projections or that these connections had already been pruned at the time points examined (E97 and later). Additional work is needed to expand our understanding of the molecular mechanisms and developmental timeline of intra- and inter-areal circuit assembly.

Modular Organization of Cortical Circuits

The concept of an elementary computational module of the mammalian isocortex was first introduced by Lorente de Nó (1933, 1949) based on anatomical studies in which he described “vertical cylinders” in the adult cortex, within which he precociously hypothesized “the whole process of transmission of impulses from the afferent fiber to the efferent axon may be accomplished.” These narrow columnar structures seen in adult cortex are now referred to as anatomical minicolumns (Buxhoeveden and Casanova, 2002) and are hypothesized to represent the vestige of ontogenetic columns seen in the developing cortical plate (Rakic, 1972). Radially oriented bundles of dendritic fibers have also been recognized as a repetitive structure in the cerebral cortex (Fleischhauer et al., 1972; Peters and Walsh, 1972) that corresponds to target-specific projections of callosal neurons (Lev and White, 1997). Dendrites in individual bundles have been shown to originate from multiple minicolumns (Peters and Kara, 1987), providing a cytoarchitectonic framework for converging information processed by many neighboring minicolumns (Innocenti and Vercelli, 2010). Functional columnar organization of the cerebral cortex was famously demonstrated by Hubel and Wiesel (1959) in the primary visual cortex and by Mountcastle (1957) in the primary somatosensory cortex of cats, where both groups found that columns, or slabs, of cells aligned perpendicularly to the cortical surface have similar feature selectivity for sensory stimuli in the environment (i.e., orientation preference in V1 or somatotopic position in S1). These findings suggest that the partitioning of the cortex into functional columns or modules is a recurrent organizational theme across species and brain regions.

Connectivity between excitatory neurons in adult cortex is highly nonrandom (Yoshimura et al., 2005), suggestive of the presence of underlying modular organization. For example, excitatory neurons in layer 5 tend to form interdigitating subnetworks composed of a few dozen highly interconnected neurons each (Perin et al., 2011). In layer 2/3 of mouse primary visual

cortex, where neurons with diverse orientation tuning preferences are arranged in a predominantly mixed salt-and-pepper configuration (Ohki et al., 2005; but see also Ringach et al., 2016), excitatory neurons with similar feature selectivity tend to be preferentially connected (Ko et al., 2011) and have stronger synapses (Cossell et al., 2015) compared to pairs of neurons with orthogonal tuning preferences, consistent with the idea that excitatory neurons are organized into functional subnetworks within the local microcircuit.

It has long been speculated that ontogenetic columns may serve as building blocks for later assembly of functional columns (von Bonin and Mehler, 1971; Buxhoeveden and Casanova, 2002; Mountcastle, 1997). However, the link between ontogenetic and anatomical minicolumns remains speculative, and a precise definition of a universal functional column is also absent, leading many to question the validity of the link between developmental and functional columns (Horton and Adams, 2005; Molnár, 2013). Across primate species, there is up to three-fold variation in neuronal density, and this number shows no correlation with total cortical area or total number of neurons (Herculano-Houzel et al., 2008), suggesting that models assuming a constant number of neurons within a given cortical area across primates (Rockel et al., 1980) are largely implausible. Nevertheless, studies in mice have found that vertically aligned pairs of neurons derived from a common progenitor are more likely to be synaptically connected (Cadwell et al., 2019; Yu et al., 2009) and have similar feature selectivity (Li et al., 2012; Ohtsuki et al., 2012) compared to nearby unrelated neurons, although the effect size varies substantially between studies (Smith and Fitzpatrick, 2012). The mechanism by which clonally related neurons form specific synapses is thought to involve transient gap junction coupling during migration (Yu et al., 2012), although other mechanisms, such as shared expression of cell adhesion molecules, have also been proposed (Tarusawa et al., 2016). Although these studies suggest that cell lineage may play a role in establishing a blueprint of functional cortical circuits, larger functional columns, such as orientation columns, are necessarily comprised of several ontogenetic columns (Rakic, 2008), and ontogenetic columns themselves are likely derived from polyclonal proliferative units (Rakic, 1988). Moreover, it remains unknown whether preferential lineage-dependent connectivity and function persist in adult animals or becomes completely overwritten by experience-dependent plasticity (Blakemore and Cooper, 1970), and whether a similar bias in connectivity and function exists among clonally related neurons in primate cortex has not yet been explored.

Circuit Dysfunction in Neurodevelopmental Disorders

A more detailed understanding how area-specific cell types and circuits emerge may provide novel insights into the pathogenesis of neurodevelopmental disorders characterized by abnormal cortical circuit assembly. Autism spectrum disorder (ASD) is perhaps one of the best studied diseases in this category and highlights both the importance and complexity of relating early realization to phenotypes that emerge later in life. Syndromic forms of autism are often associated with macrocephaly and epilepsy (Windén et al., 2018). Brain size in idiopathic autism is slightly reduced at birth, increases dramatically during the first year of life, and then plateaus such that, in adulthood, the major-

ity of patients are within the normal range (Redcay and Courchesne, 2005). Similarly, patients with idiopathic autism have increased numbers of neurons in the prefrontal cortex (Courchesne et al., 2011) and abnormal laminar architecture in prefrontal and temporal cortical areas (Stoner et al., 2014). A limited case series comparing cytoarchitectonic features between autistic and normal brains found that anatomical minicolumns are narrower and more disorganized in autistic brains compared to controls (Buxhoeveden et al., 2006). Noninvasive imaging and recording techniques, such as electroencephalography and magnetoencephalography, suggest that local connections are increased in ASD, whereas long-range connections are reduced (O'Reilly et al., 2017; Wass, 2011). Early studies using transcranial magnetic stimulation suggest that plasticity is also impaired in patients with high-functioning autism and Asperger syndrome (Jung et al., 2013). Overall, these studies suggest that early developmental mechanisms that establish proper area-specific neuronal cell types, lamination patterns, and connectivity may be disrupted in ASD and other neurodevelopmental disorders and play a critical role in the disease pathogenesis.

The genetic instabilities that evolutionarily gave rise to the developmental programs of the primate cerebral cortex may also have built-in vulnerabilities, as noted by the identification of key gene expression networks that decrease in expression over time during macaque brain development (Bakken et al., 2015). One such network enriched for genes implicated in ASD may be differentially expressed when compared to networks in human development (Bakken et al., 2015). Transcriptional comparisons of bulk sequencing gene networks and genes that have been characterized as dysregulated in autism found an enrichment of these networks during the early and peak stages of neurogenesis in subsets of excitatory neurons, specifically in the prefrontal cortex (Willsey et al., 2013). More recently, a comparative study found that the genes implicated in ASD and schizophrenia show unique prenatal expression patterns in humans compared to nonhuman primates (Zhu et al., 2018). These findings raise the hypothesis that area-specific neurons may have selective vulnerability and causal roles in the emergence of neurodevelopmental disorders. Notably, even subtle changes in the shape of the dendritic tree or the expression of certain ion channels in a subset of area-specific excitatory neurons could fundamentally alter the way neurons integrate synaptic inputs (Branco and Häusser, 2011). Mechanisms that give rise to cortical areas in normal development could go awry in neurodevelopmental disorders, and further work is necessary to understand how this happens, what genes are involved, and whether therapeutic interventions might be effective.

Biologically Inspired Neural Networks

The hierarchical organization of the cortex has inspired *in silico* models of network architecture. Biologically inspired networks serve as two-way streets, simultaneously informing both computational and experimental viewpoints (Camacho et al., 2018; Cox and Dean, 2014). Recent advances in machine learning using deep neural networks have revolutionized the artificial intelligence field in applications such as object and voice recognition (reviewed in LeCun et al., 2015). Artificial neural networks (ANNs) are vaguely inspired by the hierarchical organization of cortical areas in the mammalian cerebral cortex,

specifically the visual processing stream (van Gerven and Bohte, 2017; McCulloch and Pitts, 1990). Most ANNs are initiated using a set of initially random weights between individual nodes, and the weights are modified by backpropagation of an error signal (i.e., “cost function”) in an iterative process known as gradient descent. Backpropagation of error in biological systems was originally thought to be implausible; however, recent studies suggest that the brain could implement the error back-propagation algorithm used by artificial neural networks (Marblestone et al., 2016; Whittington and Bogacz, 2019). For example, by simply re-framing the ANN nodes as a set of dendritic events and incorporating lateral input from local interneurons, a recent study provides a potential mechanism by which neurons could implement back-propagation by increasing or decreasing synaptic strength of individual synapses within the same cell (Sacramento et al., 2018), such as might occur via synaptic tagging (Frey and Morris, 1997). As we continue to develop a better understanding of the biophysical properties of individual cells and cortical microcircuits, additional biologically plausible implementations of error back-propagation and other algorithms used by ANNs may emerge.

The performance of ANNs has recently approached or even surpassed that of humans in some tasks, in particular image recognition (Silver et al., 2016, 2017). ANNs also appear to recapitulate the general organization of functional cortical areas. For example, the layers of deep convolutional neural networks mirror the hierarchical organization of the visual object recognition pathway (Güçlü and van Gerven, 2015; Marcus et al., 2014). However, these approaches still fall short of human cognition in their ability to generalize beyond the training data and truly grasp abstract concepts, as highlighted by their failure in the face of adversarial input and the requirement for large amounts of training data (Goodfellow et al., 2014; Kurakin et al., 2016). One promising approach is to integrate unsupervised or generative models, which do not rely on labeled training data, to intuitively learn underlying patterns in the data, such as nuisance variables (Patel et al., 2015). Interestingly, recent theoretical work has also shown that incorporation of a modular architecture termed “matrix capsules,” inspired by the modular organization of the cerebral cortex, may significantly improve the accuracy and robustness of deep learning algorithms (G.E. Hinton et al., 2018, Int. Conf. Learn. Rep., conference). Large-scale efforts are underway to discover additional principles of information processing in biological brains that can be translated into meaningful advances in machine learning, such as the Machine Intelligence from Cortical Networks project funded by the Intelligence Advanced Research Projects Activity (Cepewicz, 2016). Besides areal differences in circuit architecture, subtle changes in the implementation of cost functions or error signals could be mediated by neuromodulatory inputs, such as acetylcholine or dopamine, and could contribute to area-specific computations (Marblestone et al., 2016). An improved understanding of the differences in network architecture between functionally distinct cortical areas and the developmental programs that give rise to these circuits may provide additional insights into the core features of biological networks that enable robust and efficient learning.

Concluding Remarks

Research spanning several decades has revealed substantial area-specific variations in cellular composition, lamination pattern, and circuit organization of the adult cerebral cortex. Recently, advances in single-cell transcriptomics have enabled unbiased comparisons of molecular signatures of homologous cell types across areas and suggest an updated view of serial homology during cortical development, in which molecular distinctions across broad proto-regions are established early in development and are further refined into functional areas via activity-dependent mechanisms. So far, these biological processes have largely been explored in only a few major areas, and therefore, additional studies are needed to determine what features are present as early in development as neurogenesis and what activity-dependent changes in cell identity and cytoarchitecture maturation coincide with emergence of specialized local microcircuits. The proposed model of serial homology with progressive refinement provides a more nuanced perspective of cortical arealization and may contribute to a more principled understanding of normal and pathological neural circuits.

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AUTHOR CONTRIBUTIONS

All authors contributed to writing the manuscript. C.R.C. and A.B. contributed equally.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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