8 Molecular and Cellular Mechanisms of Human Brain Development and Evolution

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ABSTRACT The immense complexity of the human brain is reflected in its cellular organization and the vast behavioral and cognitive repertoire that it can generate. The human brain develops through a dynamic and prolonged process during which a myriad of cell types are generated and assembled into intricate synaptic circuitry. Deviations from this normal course of development can lead to a variety of pathologies, including disorders, such as autism and schizophrenia, that affect some of the most distinctly human aspects of cognition and behavior. While humans share many features with other mammals, in particular with other primates, organizational and developmental differences have allowed for the elaboration of human-specific cognition and behavior. Analyzing molecular and cellular processes involved in human brain development, along with parallel studies in nonhuman primates, is necessary for defining both ancestral and uniquely human features, but this is often difficult to do in a systematic and comprehensive manner. In this review, we summarize current knowledge about molecular and cellular processes underlying human brain development and evolution. Particular emphasis is given to studies of the cerebral cortex because of its importance in higher cognition and because it has been the focus of many comparative and developmental studies.

The human brain is composed of over eighty billion neurons and at least an equal number of glial cells (Azevedo et al., 2009). Neurons are connected with approximately 150,000 to 180,000 km of myelinated axons, and within the neocortex alone, there are about 0.15 quadrillion synaptic contacts (Pakkenberg et al., 2003). These basic facts illustrate the organizational complexity of the human brain and highlight some difficulties we face when trying to understand the molecular and cellular mechanisms of its development and evolution. In this chapter, we will first review the sequences of cellular events in the developing human brain, with a focus on the cerebral neocortex, and then highlight advances in understanding the molecular processes associated with its development and evolution.

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Cellular mechanisms of human brain development

Human brain development involves many cellular and molecular processes that unfold over the course of almost two decades (Kang et al., 2011; Kostović & Judas, 2002; Sidman & Rakic, 1973; see figure 8.1). One of the most remarkable aspects of human development is that, by the time of birth, the general architecture of the brain has been assembled and the majority of neurons have migrated to their final positions. The organization of human neurodevelopment can be divided into three main sequences of events: generation of neuronal and glial cells types, migration of newly born cells to their final destination, and their differentiation into mature and properly functioning cells within neural circuits.

GENESIS OF NEURONAL AND GLIAL CELLS The ventricular and subventricular zones (VZ and SVZ, respectively) comprise the germinal zones of the developing telencephalon and give rise to neurons and macroglia (astrocytes and oligodendrocytes) of the cerebral cortex (figure 8.2; Caviness, Takahashi, & Nowakowski, 1995; Fishell & Kriegstein, 2003; Sidman & Rakic, 1973). VZ is the first germinal zone to form and is composed of elongated polarized neuroepithelial cells that undergo interkinetic nuclear migration. Early neuroepithelial progenitor cells each produce two daughter cells that re-enter the cell cycle. This symmetrical division doubles the number of progenitor cells each time and exponentially expands the pool of progenitor cells (Caviness et al., 1995; Fishell & Kriegstein, 2003; Rakic, 1995). Early in neurogenesis, neuroepithelial progenitor cells transform into radial glial cells that elongate along apicobasal axis and begin dividing asymmetrically to generate a new progenitor and a postmitotic neuron or glial cell. The generation of glial cells follows neurogenesis and peaks around birth in humans (Sidman & Rakic, 1973).

There are important species differences in the organization of neural progenitor cells and the generation

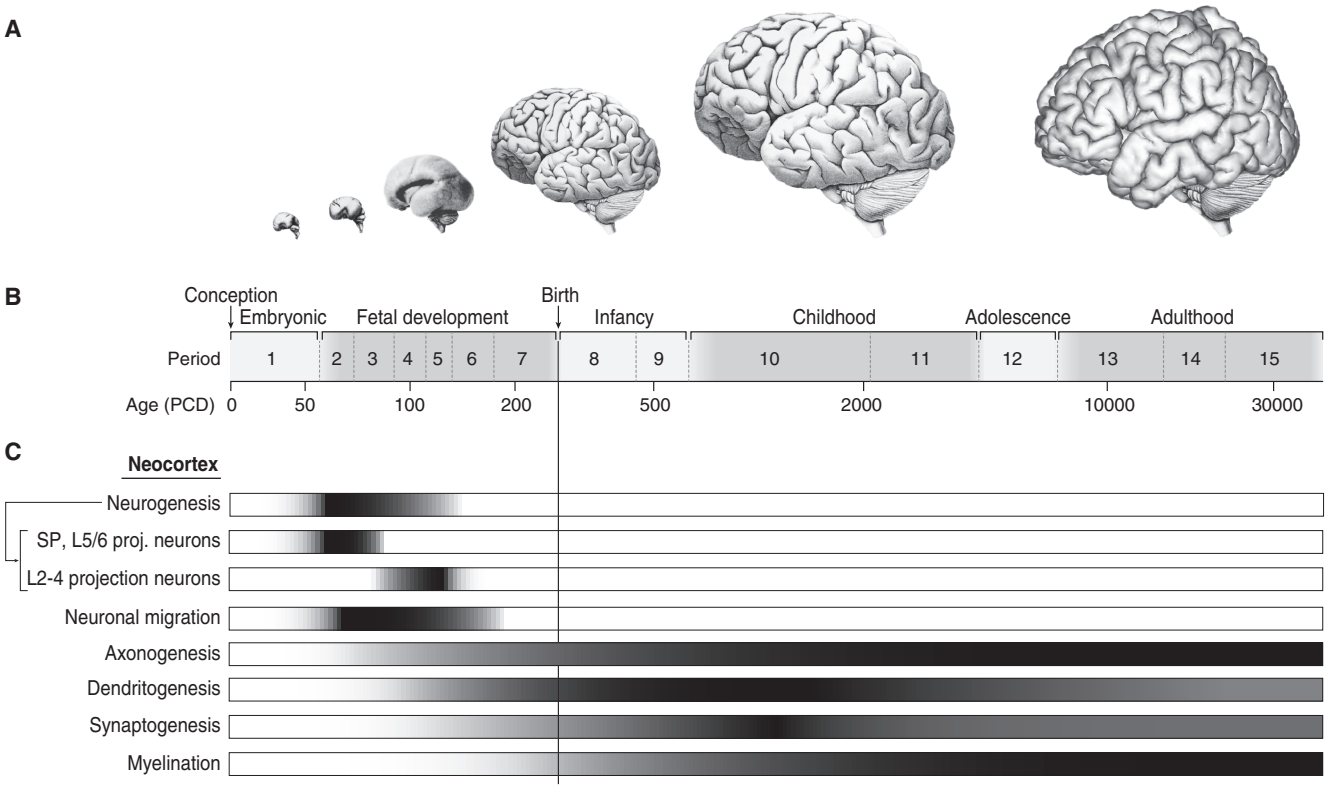

FIGURE 8.1 Timeline of major cellular events and gross morphological changes in human brain development. (A) Schematic images of developing brains from Gustaf Retzius's 1896 atlas and an adult brain generated by magnetic resonance imaging. (B) Periods of development and adulthood as previously defined (Kang et al., 2011). Age is represented in post-conception days (PCD). (C) Summaries of the occurrence and progression of major cellular events in the human neocortex. Black indicates the developmental age when the defined event reaches its peak or is indistinguishable from adult periods.

of neural cell types. One of the most prominent is the prolonged period of neuronal and glial production in humans compared to other primates and mammals (see figure 8.2), which has been postulated to play a critical role in regulating the size of the brain and maturation of neural circuits (Caviness et al., 1995; Rakic, 1995). Increases in neocortical size, particularly in primates and humans, have been linked to the expansion of progenitor cells in the outer subventricular zone (oSVZ) during development (Fietz et al., 2010; Hansen, Lui, Parker, & Kriegstein, 2010; Smart, Dehay, Giroud, Berland, & Kennedy, 2002).

There are also potential differences in the origin and migrational routes of cortical neurons, particularly between primates and rodents. The neurons of the cerebral cortex can be roughly classified into two distinct groups: excitatory and inhibitory. The excitatory neurons utilize the excitatory neurotransmitter glutamate. The great majority of them have characteristic pyramidal-shaped cell bodies and a long apical dendrite covered with spines, and project long axons to other regions of the central nervous system (Kwan, Sestan, & Anton, 2012; Leone, Srinivasan, Chen, Alcamo, & McConnell, 2008; Molyneaux, Arlotta, Menezes, & Macklis, 2007). In contrast, the inhibitory neurons or interneurons are GABAergic, form local circuit connections, and account for 15–25% of all cortical neurons (DeFelipe et al., 2013). A number of studies have shown that cortical interneurons share a common origin with striatal neurons, arising from progenitors within the ganglionic eminences of the ventral forebrain and migrating tangentially into the cortex (Marín & Rubenstein, 2003). Intriguingly, studies in humans and nonhuman primates (NHPs) have reported that certain cortical interneurons arise from dorsal, instead of ventral, pallial progenitors (Jakovcevski, Mayer, & Zecevic, 2011; Letinic, Zoncu, & Rakic, 2002; Petanjek, Kostović, & Esclapez, 2009), suggesting that the origin and migration of primate cortical interneurons are evolutionarily divergent. However, the extent of these species differences is unclear. A study of human holoprosencephaly brains, which exhibit severe ventral forebrain hypoplasia and lack a subgroup of ventral progenitors that generate distinct types of interneurons

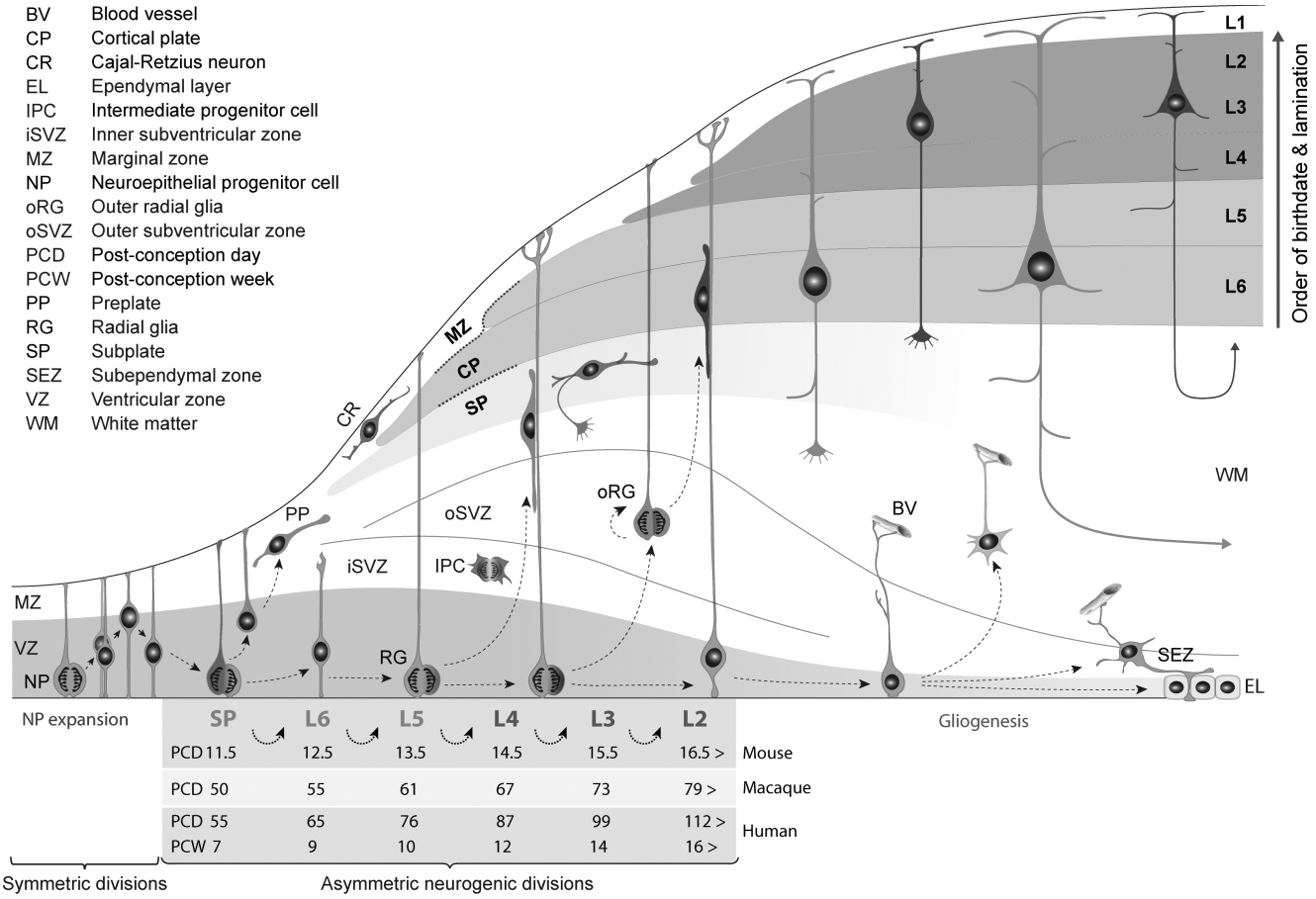

Figure 8.2 Schematic of generation and migration of projection neurons and glia in the neocortex. Projection neurons are generated by progenitor cells in the ventricular zone (VZ) and subventricular zone (SVZ). Their generation and migration into the cortical plate (CP) occurs in an inside-first, outside-last manner. At the end of neurogenesis, radial glial (RG) cells lose their polarity and generate glia. Adapted from Kwan et al. (2012). (See color plate 3.)

in rodents, revealed that these patients also lack the same subtypes of cortical interneurons (Fertuzinhos et al., 2009). Further support for the importance of the ventral forebrain in generating human cortical interneurons comes from a recent study (Hansen et al., 2010) demonstrating that cultured human neocortical progenitors do not generate interneurons.

Neuronal Migration Upon leaving the cell cycle, neurons migrate toward their final destination (figure 8.2). The first generated neurons settle immediately above the VZ, forming the early marginal zone MZ, which is also referred to as the primordial plexiform layer or the preplate (Marin-Padilla, 1978). The subsequent generation of neurons destined for the cortical plate (future layers 2–6) are thought to split the preplate into a superficial marginal zone (future layer 1) and a deep subplate zone. Neurons in the marginal and subplate zones are the first to be generated and achieve functional maturity, as well as the first to establish synaptic contacts with ingrowing cortical afferents. These neurons also play a key role in establishing cortical lamination and patterning of cortical connections (Allendoerfer & Shatz, 1994; Kostović & Judas, 2002; Rice & Curran, 2001).

Neurons use different modes of migration to reach their final destination. For example, newly born pyramidal neurons either undergo somal translocation (Morest & Silver, 2003) or migrate while attached to radial glial fibers (Rakic, 1971) to their final position in the cortical plate, following a precise inside-first, outside-last order. Hence, radial glia serves dual roles as a neural progenitor and a transient scaffold for neuronal migration. Cortical interneurons, on the other hand, migrate tangentially from the ventral forebrain or within the growing dorsal cerebral wall (Marín & Rubenstein, 2003).

In all mammals, including humans, at least two types of spatial information must be imprinted onto neurons of the developing cerebral cortex: (1) their position in

the radial direction, corresponding to their laminar position, and (2) their position in the tangential plane, corresponding to their particular cortical area. The physical separation of layers and areas is functionally determined and maintained through their distinct composition of neuronal cell types and a unique set of afferent and efferent connections. The laminar identity of projection neurons reflects their birth order, with first-born neurons occupying the deepest layers and later-born neurons present in more superficial layers. A neuron's laminar identity is also intimately linked to its eventual function; neurons of the deepest layers (layers 5 and 6) send connections to either other cortical areas or the subcortical regions, while those in upper layers (layers 2 to 4) form exclusively intracortical connections. The upper cortical layers are overrepresented in primates, especially in humans, and have been proposed to contribute to some of the cognitive and motor abilities that are unique to humans (Marin-Padilla, 2014).

Cellular Differentiation and Neural Circuit Formation Upon arriving at the cortical plate, neurons stop migrating and continue to differentiate. Despite the fact that neurons rapidly extend their axons as they migrate, most differentiation processes, such as the extension and elaboration of dendrites and the formation of synaptic connections, take place only after neurons have assumed their final laminar position in the cortical plate. Overlaid onto this laminar specification is the parcellation of neurons into distinct areas. Work in rodents has shown that the patterning is initiated by molecular signaling centers in and around the embryonic cortex (Fukuchi-Shimogori & Grove, 2001; O'Leary & Nakagawa, 2002; Sur & Rubenstein, 2005). Extrinsic influences also affect laminar and areal fate, particularly during the ingrowth of thalamocortical fibers and elaboration of cortico-cortical projections.

The timing of synaptogenesis differs across layers and regions of the developing human cortex. Synaptogenesis begins within the subplate zone and the limbic cortical areas (Huttenlocher & Dabholkar, 1997; Kostović & Judas, 2002). The earliest evidence for intraneocortical synapses has been found within deep layers at 18 post-conception weeks (Kwan et al., 2012). In early postnatal life, exuberant dendritic growth and local elaboration of axon terminals characterize a critical period during which there is a marked increase in the number of established synaptic connections and an extended capacity for neuronal remodeling in response to environmental cues and activity-dependent mechanisms (Huttenlocher & Dabholkar, 1997).

Several lines of evidence indicate that processes such as myelination and synaptogenesis progress at different rates across human neocortical areas with the general trend of earlier maturation of the primary sensorymotor areas (Giedd & Rapoport, 2010; Huttenlocher & Dabholkar, 1997).

Molecular mechanisms of human brain development

The generation of different neural cell types in proper numbers at the right time and location, followed by their assembly into a complex network, requires precise spatial and temporal regulation of gene expression. Valuable information has been obtained over the past several years by transcriptome analysis of post-mortem human brains.Transcriptome studies of the developing human brain have included a relatively small number of samples and have predominantly focused on few regions or developmental time points (Abrahams et al., 2007; Colantuoni et al., 2011; Ip et al., 2010; Johnson et al., 2009; Sun et al., 2005). Two recent studies (Kang et al., 2011; Pletikos et al., 2014) greatly expanded spatial and temporal coverage by analyzing exon-level gene expression in multiple brain regions and cortical areas across the full course of human brain development. A high percentage of genes analyzed (86%) were expressed in at least one region of the developing or adult brain. Of these, nine out of ten genes were differentially regulated at the whole-transcript or exon level across brain regions and/or time. The bulk of these transcriptional differences occurred in prenatal development. Among brain regions, the cerebellum possesses the most distinct transcriptional profile. Among neocortical areas, strong transcriptional differences were particularly prominent during fetal development and included specific transcriptional signatures associated with prefrontal and perisylvian areas, which are involved in some of the most distinctly human aspects of cognition (Johnson et al., 2009; Kang et al., 2011; Pletikos et al., 2014). These strong neocortical transcriptional differences in prenatal development diminish during infancy and childhood, and increase again after adolescence (Pletikos et al., 2014).

Gene co-expression analyses also revealed that the human developing transcriptome is organized into distinct co-expression networks enriched for specific biological functions (Kang et al., 2011). Interestingly, genetic variation in some of the most well-connected genes in these modules has previously been linked to psychiatric or neurological disorders, including schizophrenia and autism spectrum disorders, suggesting that

they may have converging functions in specific brain regions and developmental periods. The same study has also identified robust sex differences in spatiotemporal gene expression, especially prenatally (Kang et al., 2011). Some of the sex-biased genes had previously been associated with disorders that differentially affect males and females, suggesting that the risk for certain disorders may be traceable to transcriptional mechanisms.

Taken together, the above-mentioned transcriptome studies have provided unique data on the developing human brain and valuable insights into the transcriptional foundations of human neurodevelopment. As discussed in the rest of this chapter, these findings in human tissues are an important step to comparative and functional analyses aimed at elucidating transcriptional mechanisms that led to the phenotypic specializations of the human brain.

Molecular mechanisms of human brain evolution

It is often suggested that differences in expression of genes, rather than the makeup of the genes themselves, have been the major drivers of phenotypic evolution. One motivation for this claim is the argument, which is proposed on the basis of exclusion, that the protein-coding differences are too small to account for this, an idea put forward by King and Wilson (1975). However, without knowledge of how genomic changes map to phenotypic differences, it is difficult to estimate a priori what degree of divergence would be necessary in order to explain observed phenotypic differences. This difficulty is highlighted by stating the sequence differences between human and chimpanzee proteins in another way: the majority of proteins differ by at least one amino acid (Chimpanzee Sequencing and Analysis Consortium, 2005; Glazko, Veeramachaneni, Nei, & Makalowski, 2005).

An important argument for the contribution of regulatory evolution to human-specific features is that most changes are quantitative rather than qualitative, which points to changes in developmental processes and timing via regulatory evolution (Carroll, 2003; see also Hoekstra & Coyne, 2007, for a different perspective). Within the context of regulatory evolution, noncoding *cis*-regulatory evolution has been proposed as the primary source of phenotypic change, based on the idea that mutations to *cis*-regulatory regions circumvent increased selective pressure due to pleiotropic effects because regulatory elements act in a modular fashion, enabling tissue- and time-specific changes in gene-expression levels. Despite the focus on *cis*-regulatory regions, there is also evidence that transcription factors can avoid negative pleiotropy (Wagner & Lynch, 2008), making it unclear what the relative contributions of *cis* and *trans* mutations are to regulatory evolution.

Thus far, several studies have tried to globally characterize *cis*-regulatory elements that show evidence of human-specific changes compared to other NHPs. Most of these studies use conservation to gauge functional importance, as these regions have likely been preserved by purifying selection. Thousands of conserved noncoding regions show signs of accelerated evolution in the human genome (Bird et al., 2007; Pollard et al., 2006a; Prabhakar, Noonan, Paabo, & Rubin, 2006), and some regions that are highly conserved in other NHPs are deleted in the human genome (McLean et al., 2011). Global analysis of positive selection in coding and noncoding regions found that neural genes were enriched for regulatory evolution (Haygood, Babbitt, Fedrigo, & Wray, 2010). In a few cases, the ability of these regions to regulate human-specific expression has been tested using mouse transgenic assays (McLean et al., 2011; Pennacchio et al., 2006; Prabhakar et al., 2008), but the vast majority of them have unknown consequences.

As of yet, there has not been any extensive study linking human-specific *cis*-regulatory evolution to changes in human brain development. A human accelerated region (*HAR1F*) that is composed of a noncoding RNA is specifically expressed in Cajal-Retzius neurons of the cortical marginal zone in a developmentally regulated and human-specific manner, but the phenotypic consequence of this is not known (Pollard et al., 2006b). Another interesting example is *GADD45G*, a tumor suppressor gene. If a human-specific deletion neighboring this gene is introduced into the mouse, expression is no longer driven in the forebrain SVZ, leading to the speculation that this loss could have a role in human brain development (McLean et al., 2011).

A complementary approach to sequence comparisons is to compare gene expression in human and NHP brains to identify genes that are differentially expressed between species. This has the advantage of being able to identify regulatory changes regardless of the underlying regulatory mechanism. From this point, both the regulatory changes responsible for the expression change as well as the phenotypic consequences of the expression changes can be investigated.

Even though differences in gene expression during development is an area of high interest, most studies on transcriptome evolution were done in adult specimens due to the scarcity of human and NHP developmental tissue (especially from great apes) in good condition. A handful of these studies reported evidence that gene expression in the human brain has diverged

more from other primate species than gene expression of other tissues examined (Enard et al., 2002) and that there was a bias for upregulated expression in the human brain that was not observed in the other tissues (Caceres et al., 2003; Gu & Gu, 2003; Khaitovich et al., 2004). However, other studies did not find higher divergence in brain gene expression (Hsieh, Chu, Wolfinger, & Gibson, 2003) or a bias for upregulated expression in the human brain (Uddin et al., 2004). Some other works focused on differences in metabolic genes, especially in aerobic metabolism (Babbitt et al., 2010; Uddin et al., 2008), groups of genes with human-specific co-expression (Konopka et al., 2012; Oldham, Horvath, & Geschwind, 2006), and also noncoding RNAs (Babbitt et al., 2010), which were surprisingly conserved in terms of expression, suggesting that they may have a functional role.

Despite the difficulties in obtaining developmental specimens and interpreting results across species due to developmental heterochronicity (Clancy, Darlington, & Finlay, 2001), several studies have focused on analyzing gene- and protein-expression data across postnatal primate brains (Liu et al., 2012; Miller et al., 2012; Somel et al., 2009; Somel et al., 2011). An interesting finding is that the human brain, compared to the brains of other primates, appears to have an increased number of genes with a delayed expression pattern (Somel et al., 2009) and that genes involved in synaptogenesis have a prolonged expression pattern (Liu et al., 2012). Similarly, Miller et al. (2012) quantified myelinated fiber length density and myelin-associated protein expression and found that myelination is protracted in humans compared to chimpanzees. It is important to note that, while the above studies provide valuable information on human-specific expression patterns, they have used mostly postnatal samples, making them unable to detect any critical differences in the transcriptional program that shapes the human brain during prenatal development.

Functional approaches and future directions

The current feasibility of sequencing is enabling the production of an enormous quantity of data on the human and NHP genomes and transcriptomes. It is important to focus on integrating the findings at various levels and to begin to work out which species-specific differences are functionally and developmentally meaningful. Functional characterization can be approached in several ways, from using transgenic mice carrying human-specific genetic variants (Enard et al., 2009), *in utero* electroporation (Charrier et al., 2012; Kwan et al., 2012; Shim, Kwan, Li, Lefebvre, & Sestan, 2012), and human neural progenitors (Konopka et al., 2009). Induced pluripotent stem cell research is another area that may provide valuable tools for exploring human-specific features of neurodevelopment. As we advance our knowledge of the differences and the similarities in mammalian brain development, we will also be better positioned to perform informative and relevant experiments in model organisms.

ACKNOWLEDGMENTS We apologize to all colleagues whose important work was not cited because of space limitations. This article is supported by grants from the Kavli Foundation, the James S. McDonnell Foundation, and the National Institutes of Health.

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